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AMERICAN JOURNAL OF OPHTHALMOLOGY

CONTENTS

SURGICAL TREATMENT OF TUMORS AND CYSTS OF THE ORBIT*

THE ELEVENTH DE SCHWEINITZ LECTURE

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My participation in the series of lectures sponsored by this society in memory of Dr. de Schweinitz is an honor that I look upon with high regard and with appreciation of the broad interests of the ophthalmologists of Philadelphia. My training in clinical ophthalmology was acquired under the tutelage of Dr. Walter R. Parker at the University Hospital in Michigan. Dr. Parker was a University of Pennsylvania (1891) and a Wills man, and was thoroughly a Philadelphia product. Those of us who served under Dr. Parker as internes and assistants considered ourselves as somehow connected with the Philadelphia school of ophthalmology. We were concerned with the activities of the University of Pennsylvania and of Wills Hospital with an interest that could not have been exceeded if we had been serving there in residence, for our chief, a graduate of both institutions, was as much a part of them as any loyal alumnus could be. We became familiar with the names of the chiefs of the ophthalmic services in all of the Philadelphia medical colleges and hospitals, and we felt a loyalty to these men. A few years after my residency, the University of Michigan conferred the honorary degree, Master of Science, on Dr. de Schweinitz, (1923) and I held a pardonable personal pride on this occasion.

It was during the first World War, when

my chief and his close friend, Dr. de Schweinitz, served together in the office of the Surgeon General of the Army, that I met and had my first personal contact with a man whose work as a teacher and as an administrator I had come to admire. When I assumed the duties of head of the Section on Ophthalmology at the Mayo Clinic, in 1917, my first thought was to interview Dr. Parker and Dr. de Schweinitz, and the organization of the work of my section could easily be recognized as a grandchild of the Philadelphia-Michigan system.

May I say now that the invitation to address you on this occasion seems to me like an invitation to attend a family reunion as one of the poor relations, but one who, nevertheless, has his heart in it. To the section, and your committee on selection of speaker for this occasion, I humbly offer my sincere thanks for thinking of me.

The possibilities of improved surgical treatment of tumors of the orbit have intrigued general surgeons as well as ophthalmologists during the period of development of surgical practices for the relief of blindness and other ocular disturbances resulting from abnormal growths about the visual pathways. The anatomic limitations of the orbit are definitely set by its bony walls, and the field of surgical procedures by the ophthalmic surgeon has been thereby limited.

Neurosurgeons, however, have accepted no such limitations to their field of activity. Late comers to the field as they are, never-

theless, their progress has been remarkable in the field of ophthalmology. The general surgeon has abandoned the central nervous system and its disorders to this newly specialized group of surgeons, and now the field of surgery of the head is allocated to the neurosurgeon, the ophthalmologist, and the otorhinologist.

Unfortunately the anatomic barriers of the orbit that have so clearly defined the surgical field of the ophthalmologist have not limited the extent of involvement of pathologic processes that disrupt functions of the brain and especially involve the eye and the orbit. The diagnosis of these processes for the most part has remained within the province of the ophthalmologist and, in collaboration with the neurosurgeon, the newer methods of surgical treatment have brought about most gratifying results in conservation of vision and in the treatment of many of the tumors and cysts that affect the visual pathways.

Diagnosis of tumors of the orbit

Space-taking lesions within the orbit produce exophthalmos. The amount of proptosis of the globe and direction of its displacement only in general indicate the size and position of the lesion within the orbit. The rigid orbital walls constitute a barrier to expansion of a lesion but do not prevent extension through the bone of such tumors as meningioma and hemangioma.

The onset of proptosis may be an early or a rather late sign of an intraorbital growth. A tumor that grows readily within the orbit forces a change in the position of the eye within a few days or weeks but, in some cases of orbital tumor, it has been observed that, due to its slow development and adjustments within the orbit, proptosis and lateral displacement of the globe occur only after the tumor has reached a size equal to that of the globe or larger. However, in such cases, when proptosis finally occurs, it is usually marked and rapidly progressive.

The extent to which the optic nerve and the extraocular muscles may be pushed aside is quite remarkable in some cases of slow-growing tumors. A minimum of disturbance of visual function is sometimes seen in an orbit which contains a tumor of such size that it seems unbelievable that it could exist without producing more obvious displacement of the globe.

The question of extraorbital extension of a tumor is always present and seldom easily answered before surgical intervention. This is particularly true of tumors situated in the posterior portion of the orbit.

Types of tumors that are common to both the orbit and the cranial cavity, such as endotheliomas, may be present in both places. Hemangiomas and endotheliomas that arise within the orbit are not always limited to the orbit but may extend into the cranial cavity or the paranasal sinuses with little discernible evidence of their having done so. Obviously surgical treatment of such conditions must be planned on a basis broad enough to care for any extension that may be found. Failure to do so has resulted in many surgical tragedies.

As has been pointed out by Spaeth[1] and other writers on orbital surgery, the common factor of all space-taking lesions of the orbit is exophthalmos, so it is quite clear that exophthalmos, particularly when it is bilateral, cannot always be an indication of neoplasm. Inflammatory diseases of the orbit, Mikulicz's disease, and some of the blood dyscrasias also produce exophthalmos.

Metabolic diseases, especially goiter, are usually recognized by general systemic changes in addition to the ocular signs which in most instances are bilateral. Although the exophthalmos is distinctive in some cases of hyperthyroidism and the exophthalmos may be accompanied by lid retraction, chemosis, and disturbance of the function of the extraocular muscles, goiter is not usually considered in the case of a patient who experienced none of the systemic symptoms of the disease. Yet, in a patient whose history is negative for exophthalmic goiter and whose

basal metabolic rate is normal, unilateral exophthalmos due to toxic goiter is not uncommon, as is shown by the changes in the extraocular muscles seen on microscopic examination.

The difficulty of distinguishing between tumor of the orbit and the inflammatory and metabolic causes of exophthalmos cannot always be overcome even with all of the refinements in diagnosis. In such cases, surgical exploration of the orbit may be justified on a presumptive diagnosis of tumor, when there are no important contraindications to operation and when loss of vision or other serious damage seems imminent.

The orbit may be explored by several methods of approach without much risk to life or vision and with little or no resulting deformity. Indeed the involved surgical risk may be a small price to pay for the advantage of a confirmed and accurate diagnosis because, in the treatment of malignant neoplasms anywhere in the body, there is a great advantage in early acquisition of all information by whatever means.

Exophthalmos is not the only indication of space-taking lesions of the orbit. Disturbance of ocular motility and loss of vision, existing either alone or together with exophthalmos, are common to tumors and cysts of the orbit and to cellulitis, pseudotumors, and trauma. Often several confusing and contradictory signs appear that make it impossible at a given moment to make a definite diagnosis. The conditions involved are probably more common in the experience of the ophthalmologist than of the neurosurgeon and the decision on surgical intervention must be left to the ophthalmologist when the significance of the orbital signs are inconclusive and the cause is in doubt.

SURGICAL PROCEDURES

It is incumbent on the ophthalmologist to determine when surgical treatment of orbital disease is indicated and what type of approach can be used to the best advantage.

The latter requires judgment based on experience because of a dual purpose in operating. If the condition suspected is found, the operation serves as means of a cure but, if something else besides the suspected condition is found, the surgeon must be prepared and equipped to proceed to do what is necessary and to complete the operation, if possible, rather than to withdraw from the field after a fruitless entry. The opening of the orbit for biopsy only is poor practice and should be discouraged.

Of the surgical approaches to the orbit, the most direct is through the outlet, the anterior opening.[2] Resection of the lateral wall of the orbit is but a modification that is useful in certain cases. "For the removal of tumors that are definitely confined to the orbit, even in the posterior third, the frontal or the Krönlein operation may be entirely adequate, as has been proved many times. However, one seldom can be certain that a tumor known to be in the apical portion of the orbit does not extend beyond the orbital walls, or where its origin might be."[3]

The orbit, from the standpoint of surgical approach, may be roughly divided into an anterior third, posterior or apical third, and a middle portion. The entire orbit may be explored through a frontal approach, but the removal of a tumor originating in the posterior one third of the orbit or of a tumor of the optic nerve without removal of the eye is extremely difficult. If the transcranial approach is used, the task is less complicated.

Tumors of the anterior third, particularly of the lateral and inferior portions, as well as those that lie along the superior wall, can be most satisfactorily removed by way of the frontal or the frontolateral approach.

Tumors of the posterior third can be reached more directly by a transcranial approach where the operator can work under direct vision. The transcranial route permits full exploration of the orbit after removal of the roof, and it is possible to explore the orbit further anteriorly by direct vision

through the transcranial route than it is to explore the apical portion backward through the orbital outlet. Adequate removal of tumors that arise within the orbit and extend through bone or through the fissures into the cranial cavity can be accomplished only by the transcranial route. By this method, resection of the entire roof and the lateral wall of the orbit and uncovering of the op-

Fig. 1 (Benedict). The incision is made through the skin and periosteum parallel with and 5 mm. above the rim of the orbit on the superior temporal side. (Republished with permission. From Benedict, W. L.: Removal of orbital tumors. Surg., Gynec. & Obst., 58:383-389 [Feb. 15] 1934.)

tic canal is often necessary and can be done without serious damage to the orbital contents.

The attempt to save all ocular function as far as possible makes it necessary to dissect close to the tumor within its capsule and, when the frontal approach is used, much of the dissection must be done by touch rather than sight. The important matter is to remove the tumor with as little trauma as possible and leave the question of the origin of the tumor to be decided after the histopathologic examination. Immediate pathologic examination of frozen sections has proved to be most helpful in determining

how extensively the resection of tissue surrounding the tumor should be carried out.

SURGICAL ZONES

Within the orbit the anatomic structure of the soft tissues forms three divisions: the subperiosteal, the intramuscular cone, and the space between the two. Tumors or cysts arising within any one of these divisions tend to expand within fibrous capsules or delimiting membranes, pushing aside surrounding structures without actually infiltrating them and, for the most part, they tend to remain within the zone in which they originate. The chief exception to this rule is the metastatic or invading carcinoma of the mixed basal-cell and squamous-cell type; also, the dermoid and some forms of neurofibroma are exceptions.

It is not my intention to describe the technique of various surgical operations on the orbit, except as it is necessary to the understanding of a surgical procedure recommended for a special purpose.

The size and position of a tumor lying in the anterior third of the orbit will largely determine the method of frontal approach. Such a tumor obviously lies outside the muscle cone. The greater number of tumors in the anterior part of the orbit lie above or temporal to the globe and can be reached by direct frontal approach. A large number of the tumors in this region are encapsulated hemangiomas, low-grade adenocarcinomas, and neurofibromas.

One method of approach is through the conjunctival cul-de-sac along the temporal rim of the orbit after a small canthotomy. Since the tumor lies outside of the muscle cone, it is not necessary to divide the external rectus muscle as illustrated in some texts and motion pictures. The tissues are flexible and the eye can be pushed aside and rotated toward the nose, affording plenty of room for operating.

After exposure of the tumor by sharp dissection, it should be separated from its capsule by blunt dissection and delivered

by gentle pressure from below by the blades of blunt scissors or a hemostat. Adherent tissue, including the capsule, should be trimmed close to the tumor and left in place. Unnecessary damage to the surrounding tissue should be avoided. The incision may be closed without drainage and a pressure dressing applied until danger of bleeding is past. Full recovery without deformity or difigurement usually follows with a minimum of inflammatory reaction.

Moderately large encapsulated tumors of the lacrimal fossa, those situated in the dome of the roof, and those along the nasal wall may be reached more easily by the frontal approach through a brow incision.[4] I have described the technique of this operation elsewhere and an illustrated description of the method appears in Spaeth's textbook on ophthalmic surgery (page 95—figures 1, 2, and 3). This method is also used for extraperiosteal tumors.

For the removal of any tumor that should be removed by the frontal route, adequate space is made available by depressing the orbital contents. If the tumor is found to be too large or extends too far posteriorly for separation and removal in the available space, the frontal wound should be closed and the transcranial or some other suitable route employed.

Resection of the lateral wall of the orbit (Krönlein's operation) affords a little more room to work than the frontal route through the brow incision. It is most helpful in operating on orbits with small outlets for tumors situated in the posterior third of the orbit.

Tumors of the optic nerve have been successfully removed with preservation of the eyeball by the Krönlein method. Successful removal of tumors of the optic-nerve sheath, with preservation of vision, by the Krönlein method has been reported, but we now know that such tumors can be more easily removed under direct vision by the transcranial operation.

Although it is not possible to know the type of tumor, the size, and its probable situation, and, in some cases, whether it extends beyond the walls of the orbit can be determined with reasonably certainty. Some types of tumors predominate in one of the three anatomic devisions.

In the muscle-cone zone, tumors of the optic nerve and its sheath, endotheliomas, and the extension of retinoblastomas along
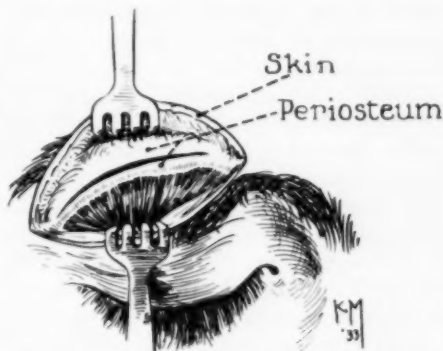
Fig. 2 (Benedict). The periosteum along the orbital rim and its extension, the periorbita, are separated from the bone with a nasal septal elevator. (Republished with permission. From Benedict, W. L.: Removal of orbital tumors. Surg., Gynec. & Obst., 58:383-389 [Feb. 15] 1934.)

the optic nerve predominate.[5] Metastasis of carcinomas to the optic nerve have been reported but are rare. Tumors situated in the muscle cone are characterized by progressive proptosis, early visual loss, and edema of the lids without lateral displacement of the eye. Movements of the eye are not usually impaired to the extent of producing diplopia. We have not encountered bilateral tumors of this type, but bilateral orbital tumors can be removed in one stage by utilization of the coronal or Souttar flap.

In the subperiosteal zone the most common tumors are osteomas, which have their beginning in the paranasal sinuses, and meningiomas that extend into the orbit from the cranial cavity.

The term, "osteoma," should be reserved for the bony tumors of the sinuses which

invade the orbit. They are always rounded and covered by a mucous membrane continuous with the lining of the sinus from which they originate. They are said to expand along the lines of least resistance and are to be found in the cranial cavity or the orbit or both. They are, of course, extraperiosteal and extradural. A large osteoma of the orbit may extend well into the cranial cavity, push the dura-covered cerebrum before it, and erode the frontal bone, and yet produce no signs or symptoms except exophthalmos.

Osteomas are pedunculated on a base in the thin walls of the sinus and are, as a rule, easily removed by dividing the peduncle. Recurrences are rare. Osteomas of the orbit are objectionable only when they become large enough to cause proptosis, or in some manner to interfere with the movements of the eye. They grow very slowly and removal is not an urgent matter.

In our series of orbital tumors there were 38 osteomas of the orbit, 19 of which were operated on and removed by the frontal method with no fatality. One patient had postoperative rhinorrhea and died of meningitis two years afterward.

Hyperostosis of the bones of the orbit when accompanied by thickening of several bones of the skull, especially the facial bones, is not a surgical condition; acromegaly is an example. The roentgenogram shows very clearly the type of bone disturbance in any case of bone tumor but the diagnosis is always clearer in osteoma than in hyperostosis from any cause because of the distinct outlines of the osteoma and the absence of other than local symptoms.

Of the three bony disorders of the extraperiosteal division, only the osteoma can be removed by the frontal route. Hyperostosis and exostosis call for transcranial surgical removal.

The bony roof is sometimes eroded by cranial meningiomas but in 25 percent of cases the bone is infiltrated by the tumor and hyperplasia appears in the roentgenogram as hyperostosis. This is an important diagnositic sign of cranial meningioma but not pathognomonic, since vascular tumors may also produce such a hyperostosis.

When hyperostosis of the sphenoidal ridge is present, one cannot say whether the tumor originated within or outside the orbit. Very seldom, however, does a meningioma arising within the orbit produce a hyperostosis of the sphenoidal ridge. Therefore, in patients who do present hyperostosis of the orbital roof, the frontal method of approach is contraindicated.

Prior to the introduction of the transcranial method of approach to the orbit, complete exenteration of the orbit was done for orbital tumors even with extensive hyperostosis. The results of the operations were not encouraging, for in no instance could the entire tumor be removed. Bone tumors of the orbit other than hyperostosis can usually be completely removed by the frontal approach through a brow incision as previously mentioned.

The greatest number of primary tumors of the orbit arise in the middle zone, between the periorbita and the muscle cone. It is often impossible to trace the origin of an orbital tumor but, in most cases, one can say that it was situated in one of the three anatomic divisions.

From the records of the Mayo Clinic it has been shown that in the years 1907 to 1947, inclusive, there were 3,190 patients who had tumors of the eye or the adnexa or both, of whom 740 had tumors of the orbit. Thirty-three types of tumors were diagnosed pathologically, while a few were indeterminate. Most of them were primary tumors of the orbit in various stages of development. Operation was performed on a total of 420 by methods best designed to meet the demands of the situation. The transcranial method was employed in 48 cases from November 6, 1933, through December 31, 1947. Analysis of data on orbital tumors removed transcranially showed that in 28 cases the tumor was entirely within the orbit;

whereas, in 17 cases there was intracranial extension. In 3 cases there was extension into adjacent bone or into the frontal sinus and in 1 case even into the nose. There was only 1 death in the series.

A comprehensive report on the menin-

and must be differentiated from intraorbital tumors. They may have extended into the orbit through an enlarged superior orbital fissure or by destruction of the bone and penetration into the orbit.

In 17 cases, primary intraorbital menin-
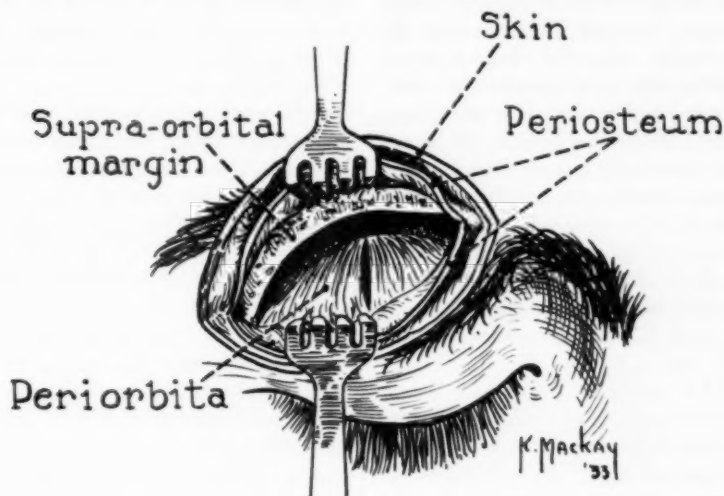
Fig. 3 (Benedict). The periorbita is pulled forward and down so that the contents of the orbit can be palpated and the tumor located. The incision through the periorbita can be made at the most advantageous place. On closure of the wound, the edges of the periorbital incision are reunited with catgut, the periosteum is reattached above the rim of the orbit with fine catgut, and the skin incision is closed with silk. The skin does not come in contact with the bone, and so, deep scarring is avoided. (Republished with permission. From Benedict, W. L.: Removal of orbital tumors. Surg., Gynec. & Obst., 58:383-389 [Feb. 15] 1934.)

giomas of the orbit operated on at the Mayo Clinic shows that the origin of these tumors still is a somewhat controversial subject. Whether they are truly primary growths arising from the coverings of the intraorbital part of the optic nerve, and possibly from the other structures within the intraorbital cavity, or whether they merely extend into the orbit from a similar growth within the cranium has been, and still is, a moot point.

As was clearly brought out by Cushing, meningiomas possess a tendency to expand along lines of least resistance and force their way into "all anatomical crannies and pockets." Meningiomas of the sphenoidal ridge may cause unilateral exophthalmos

giomas have been recognized and treated surgically at the clinic. All were verified microscopically and were studied carefully to establish their identity as essential primary intraorbital growths. The presenting clinical signs and symptoms consisted of visual impairment, a measurable proptosis, and headache. Either visual failure or proptosis or both were present in every instance. Visual impairment was present in 14, proptosis in 13, and headache in 5 cases.

In 35 cases, meningiomas were found to have invaded the orbit from an intracranial source. In both groups the lesions were more common in women than in men by a ratio of 4:1.

This series suggests that primary tumors

are likely to be encountered at much the same age as are secondary, or invading, neoplasms, and as are meningiomas elsewhere. The order in which proptosis and visual impairment may appear does not serve as a reliable aid in distinguishing the intraorbital meningiomas from other intraorbital lesions. Roentgen changes about the orbit are usually suggestive of an invading type of intraorbital meningioma. The transcranial route of approach best meets any contingencies which may arise in the attack upon these tumors.

The greater number of orbital tumors of this series of 490 cases were removed by the frontal approach. They were situated mostly in the middle division of the middle and anterior zones and were operated on by whatever method gave promise of the best results.

Of the 420 operations for orbital tumor, 32 were for epithelioma of the face with secondary involvement of the orbit. Some began as epithelioma of the eyelids, others of the caruncle, that extended into the orbit along the periosteum after repeated excisions, cauterization, and irradiation had failed to halt their progress.

Epitheliomas of the squamous-cell type are prone to extend to bone where they become fixed. They not only spread along the periosteum but actually invade the bony walls of the orbit causing marked necrosis. Extensive removal of bone sequestra and cauterization of the soft parts must be carried beyond the limits of tumor invasion. Exenteration of the orbit was required in 7 of the 32 cases. Surgical removal of neoplastic tissue may be followed by irradiation with good effect.

Generalized metastasis from squamous-cell epithelioma is rare, although occurrence of other primary neoplasms of different types is not uncommon. Adenocarcinoma of the breast and neurocytoma of the brain were seen as examples of primary tumors following some years after exenteration of the orbit, in one case for squamous-cell

epithelioma and in another for melano-epithelioma.

The frontal approach was used in 340 cases of orbital tumor. In this group, there were 40 exenterations of the orbit for extensive neoplasm and 10 were by the Krönlein method. These tumors had their origin within the orbit. These included, somewhat in order of their frequency, carcinomas, sarcomas, hemangiomas, dermoid cysts, endotheliomas, and a number of rare tumors encountered only 1 to 5 times in the series.

The most common location of carcinomas was in the superior temporal quadrant. For the most part they were associated with the lacrimal gland or the accessary lacrimal glands and were of two types, mixed tumors and cylindromas.

The adenocarcinomas occurred in a variety of sizes and degrees of malignancy. Many of them were entirely encapsulated, were only loosely attached to the lacrimal gland, and, when removed, showed no tendency to recur. The most malignant type of adenocarcinoma becomes fixed to the bony orbit through the periosteum early in its course and, by the time exophthalmos is produced, the tumor has spread well back along the walls of the orbit and in many cases has invaded the bone as well. Such tumors maintain their glandular activity and, as they progress by direct extension, will form cysts of considerable size.

One patient with adenocarcinoma of the orbit was reoperated on 3 times at 5-year intervals. At the second and third operations, only a small amount of neoplastic tissue was found, but between the skin and the dura much of the frontal bone had sequestrated and in this region cysts containing 1 to 3 ounces (30 to 90 cc.) of fluid were formed.

The adenocarcinomas that arise in the orbit expand by direct invasion of neighboring tissue but seldom give rise to generalized metastasis. The so-called mixed tumor grows more slowly, is less malignant, and is not accompanied by the severe necrosis of bone as seen in other types of carcinoma.

In this series of eye tumors there were 43 metastatic tumors, 19 of which reached the orbit but only 1 of which was removed. Most of the metastatic tumors were carcinomas from the stomach, breast, and intestinal canal. All were highly malignant and were seen late in the course of the disease as a part of general metastasis.

Melano-epitheliomas are common about the lids, conjunctiva, and the uveal tract. They form a very interesting group of tumors that have their origin in and about the eye and invade the orbit by direct extension. Of 333 patients who had melanomas, benign and malignant, 12 percent had tumors of the orbit.

In a few cases the orbit was invaded by direct extension through the sclera from melanomas of the choroid. Others were primary in the caruncle and conjunctiva. A few melanomas were found deep in the orbit and, so far as could be determined, were primary tumors. It is unfortunate that we have no way of determining the degree of malignancy of melanomas. One cannot predict from the microscopic appearance of a melanoma whether it will metastasize or remain dormant.

I have reported elsewhere on a patient with extensive malignant disease of the right orbit with deep melanosis of the conjunctiva, the mucous membrane of the mouth, nares, and nasopharynx of the same side. Exophthalmos was noted when the child was about 8 years of age. By the time he was 14 years of age, and after several years of roentgen therapy, the right orbit was exenterated because of a large melanoma which caused extreme exophthalmos and loss of the cornea. A complete exenteration of the orbit was done but necrotic pigmented tissue remained at the fissures and the apex and could not be removed. Tissue removed was diagnosed as Grade 4 melano-epithelioma. After 20 years, the orbit gradually has filled in and the outlet is practically covered by skin. The melanosis of the mucous membrane of the nose and the mouth

remains practically unchanged and there has been no extension, no recurrence, and no metastasis.

In another patient the right eye was removed because of an intraocular neoplasm shown to be malignant melanoma. The sclera was perforated in many places by the neoplasm which, however, did not extend deeply into the orbit. At the time of enucleation, the orbit was clean. Within six months after the enucleation, the conjunctiva of the socket was studded with 8 isolated, deeply pigmented nodules of melanoma that were from 3 to 8 mm. in size. For the past six years there has been no change in the size or appearance of these melanomas. The patient wears an artificial eye but there is no evidence that the pigmented nodules are irritated by rubbing. There are no metastatic lesions anywhere in the body and the patient is, so far as general examination shows, entirely free from evidence of melanoma elsewhere in the body.

These rather extreme examples of arrest of what appeared to be Grade 4 malignant neoplasms are not explained by histopathologic examination of the tissue. The malignancy of the neoplasm bears no relation to the amount of pigment contained. There is ample clinical evidence to show that in some individuals melanomas take on a high degree of malignancy and give rise to extensive metastasis and, in others, the growth of malignant neoplasms becomes halted and their activity is stationary, at least for a number of years. Except for melanomas of the uveal tract which are most commonly limited to the eyeball, there is very little clinical or histopathologic indication for wide surgical removal of melanotic tissue.

The very rapid and extensive metastasis of melanomas in other cases illustrates the reverse of arrested development. This tendency to accelerated extension of melanomas has been known to set in several years after removal of an eye for tumor of the uveal

tract and without activation of any other known primary source.

This wide difference of the tendency of melanomas to remain dormant indefinitely, or to become reactivated after a number of years, and to flare immediately into violent activity by direct expansion and metastasis, opens speculation as to whether there is an immunity present in some persons and not in others, and whether immunity is developed in some cases and lost in others.

The clinical behavior of melano-epitheliomas is peculiar in the field of malignant neoplasms. It would seem that their origin and their true nature have not yet been satisfactorily explained. The key to further understanding of cancer may well be found by research in this type of tumor.

Hemangiomas of the orbit constitute a group of vascular tumors of which there are a number of structural types and histopathologic variations. Usually situated in the middle division of the orbit, they may simulate meningiomas by causing erosion of the orbital walls or hyperostosis.

In the series of 3,190 eye tumors, 205 were diagnosed as angiomas of some type and 64 were located in the orbit. Thirty-three were diagnosed as hemangio-endotheliomas. They were more frequent in the posterior part of the orbit where they were sometimes confused with dural endotheliomas.

These endotheliomas are quite similar in their clinical characteristics as well as in their histopathologic features. They are highly malignant and extend by expansion along anatomic structures into every part of the orbit where nerves and blood vessels run. They are seldom encapsulated, are difficult to remove, and prone to recur, and are particularly resistant to irradiation. In common with other hemangiomas they are more frequent in persons under 25 years of age and often assume sufficient size to warrant surgical removal before the age of puberty.

The prognosis in hemangio-endothelioma

is always grave. Complete surgical removal is imperative wherever possible. As they are clinically indistinguishable from other types of endotheliomas and usually occur within the posterior third of the orbit, they come within the field of the neurosurgeon and are removed by the transcranial route.

The greater number of vascular tumors of the orbit are made up of a proliferation of small vessels and a mass of fibrous tissue. Many of them are encapsulated, firm, fibrous, rounded masses that have scant blood supply and grow slowly. They are benign, do not give rise to metastasis, and do not recur after surgical removal. They are frequently found in children, rarely, if ever, arising after middle age. The prognosis in such cases is good.

Another type, however, that is troublesome for the surgeon is the cavernous angioma. This tumor is made up of thin-walled vessels, mostly on the venous side, and may be similar in most respects to a venous aneurysm. Since it occurs most frequently in children, it probably is congenital.

The tumor develops slowly under normal conditions. The cavernous spaces hold considerable blood, almost stagnant, which becomes noticeable only when thrombosis occurs. Under this condition the mass increases to the extent of elasticity of the affected vessels and there constitutes a space-taking lesion, as would any kind of tumor of equal size. Exophthalmos of several millimeters comes on within a few hours. There is edema of the lids and, after a few days, discoloration of the skin of the lids. Chemosis is usually mild.

If unmolested, the venous walls give way, a break occurs, and the contained blood, which has become a thin black fluid, escapes into the surrounding tissues and is absorbed. The exophthalmos subsides and all signs of tumor disappear. However, recurrence is common. In patients who have undergone operation the prognosis must be guarded.

The gross appearance of the tumors in

the surgical field is that of a tangled mass of thin-walled vessels, several millimeters in diameter, and filled with dark blood. The mass is surrounded by a number of thin, fibrous sheaths with septa weaving among the vessels to provide a frail supporting framework.

In trying to dissect such a tumor, nicking or rupture of a vessel wall usually occurs, whereupon the mass collapses, the bloody fluid escapes, and the tumor becomes indistinguishable from its fibrous sheaths. It is hardly ever possible to remove it entirely. Recurrence of the angioma is the rule. The varicosity of the vessels slowly progresses and extends even beyond the orbit's walls.

An angioma of this type, which involved both the orbit and the cranial cavity and clinically resembled a meningioma in its roentgen aspects, was a notable one in this series. It was a clear demonstration of the possibility of hyperostosis of the sphenoidal ridge by a tumor other than meningioma.

The cavernous type of hemangioma is not a malignant neoplastic disease in that it induces necrosis in tissue. However, areas of calcification shown in the roentgenogram speak for pathologic processes that may lead to disturbance of ocular function.

CONCLUSIONS

It is seldom that one can make a diagnosis of any particular type of orbital tumor from clinical evidence alone. In some cases one cannot distinguish between a tumor, a cyst, a venous aneurysm, a pyocele of the paranasal sinuses, toxic goiter, or inflammatory and metabolic disease with orbital involvement.

When all methods of differentiation have been utilized, the surgeon must decide whether exploration of the orbit is necessary and what method or route is best suited. The deciding factors are these: the threat to vision; the probable location and extent of the lesion; the evidence of growth and metastasis; and the age and general condition of the patient.

The threat to vision is probably the most important reason for surgical exploration of the orbit in cases of space-taking lesions. Progressive loss of visual acuity, with or without changes in the visual fields, may be the outstanding sign of orbital tumor, and surgical treatment may be the only means of preventing blindness. There are indeterminate lesions that do not demand immediate surgical intervention because there is no definite threat to vision, and roentgen therapy and medical treatment, under observation, may prove to be satisfactory treatment.

Loss of vision, exophthalmos, disturbance of motility, and impairment of function of the eyelids must be carefully observed for signs of expansion or growth so characteristic of tumors and cysts. The choosing of the optimal time for surgical intervention is often a difficult problem and even the most experienced surgeon will make mistakes.

The one admonition that my experience in dealing with more than 700 surgical cases of ophthalmic tumors and cysts points to is that of preparedness to complete the necessary surgical treatment involved in any attempted operation and to refrain from meddlesome interference to satisfy curiosity in indeterminate cases.

The Mayo Clinic.

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LOCAL USE OF HEPARIN IN THE EYE*

PELLET IMPLANTATION AT AN EXPERIMENTAL FILTERING SITE

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The desirability of using heparin to prevent postoperative fibrosis after glaucoma surgery was mentioned in a previous paper.[1] Methods of heparinization of the eye were investigated and it was shown that heparin did not enter the primary aqueous. It was concluded that direct local introduction of heparin would be the most efficient and practical means of heparinizing the eye. This study concerns the local use of heparin in the form of pellets and the results obtained from the implantation of such pellets at the site of an experimental filtering operation. Observations on the local absorption of heparin are made.

PREPARATION OF PELLETS

The preparation of pellets of sodium heparin for local use was undertaken to provide a readily controllable mass of heparin to remain at a local site for a longer period of time than the heparin powder or the heparin solution.

The following technique was employed for the preparation of heparin pellets. Powdered sodium heparin was loaded into one end of a cellophane soda straw for a distance of about 1 cm. The open end was moistened with a few drops of distilled water until the heparin powder melted. A mosquito clamp was placed distal to the heparin mass to prevent it from running down the cellophane tube. The segment of tube containing the wet heparin was placed in a vacuum dry-

ing jar for 24 hours. The cellophane was then easily peeled off and the pellet of fused heparin was removed, weighed, and placed in absolute alcohol for storage.

Pellets remaining in absolute alcohol lost no weight in three months. The pellets were cylindrical in shape with tapered ends and were quite brittle. They varied in weight from 60 to 34 mg. each, with an average weight of about 45 mg. Before use, the pellets were air dried on a sterile towel to remove the alcohol.

ABSORPTION OF HEPARIN PELLETS

Two experiments using heparin pellets were undertaken to determine the rate of solution of heparin in the intraocular fluid of the rabbit. An anterior-chamber implant of a 41-mg. pellet dissolved completely in 21 minutes, while 66 mg. of sodium heparin dissolved in 41 minutes. In order to insert a pellet of the latter size, it was necessary to dislocate the lens backward slightly. Subconjunctival implants of 43- and 55-mg. pellets dissolved in an hour and an hour and 15 minutes, respectively. In these experiments, there was no local inflammatory reaction.

In Figure 1, a comparison is made between an intravenous dose of heparin of 25 mg. per kilogram and a similar dose in the form of a subconjunctival pellet implantation. When the heparin is given intravenously, the anticoagulant effect reaches a maximum immediately and is almost dissipated at six hours. In the case of the subconjunctival pellet, six hours are required for the maximal anticoagulant effect.

Heparinization of the blood stream per-
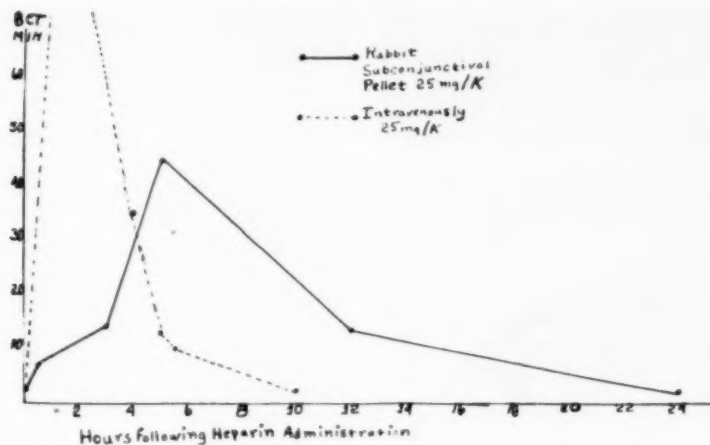
Fig. 1 (Bick and Haines). Anticoagulant effect of intravenous heparin and a subconjunctival heparin pellet implant.

sists for 18 to 24 hours after pellet implantation. If a similar pellet is implanted at the site of a filtering operation (fig. 2), there is a delay in the appearance of heparin in the blood stream and a maximal clotting time is reached in two hours.

The anticoagulant effect of a pellet of 34 mg. (15 mg./kg.) implanted at a filtering site is also plotted in Figure 2. Both curves represent heparin which is released from the local site in excess of the capacity of the tissues to hold heparin. With pellets smaller
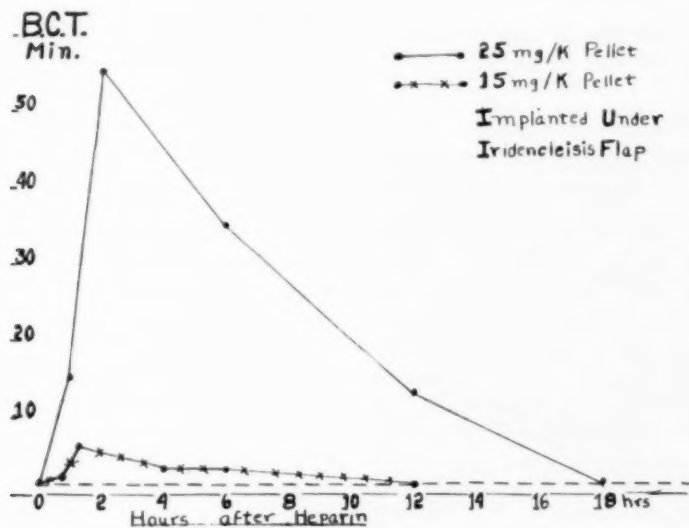
Fig. 2 (Bick and Haines). Anticoagulant activity of heparin pellets placed at the site of an iris inclusion operation. The lower curve indicates tissue saturation with a slight excess of heparin. The upper curve shows a considerable excess of heparin.

than 30 mg., no anticoagulant effect is noted. Consequently, the tissue saturation dose for a pellet implantation is about 30 mg. For purposes of tissue saturation, pellets in excess of this may be regarded as wasted heparin.

It is interesting to study the rapidity with which the heparin enters the blood stream

Fig. 3 (Bick and Haines). Heparin implant at site of filtering operation. The conjunctiva is sutured well behind the implant.

according to the site of implantation. If heparin is placed directly into the anterior chamber by injection of a saturated solution, a maximal effect is noted in the peripheral blood in one hour.[1] With pellet implantation at a filtering site (fig. 2), the time is lengthened to two hours; whereas, a simple subconjunctival implant (fig. 1) delays the maximal effect to six hours. It would appear, therefore, that the wash of aqueous through the filtering operation is instrumental in carrying heparin through the channels by which it is absorbed into the blood stream.

This wash of aqueous saturated with heparin is sufficient to prevent the local formation of fibrin in the absorbing channels for at least 18 hours and probably for several hours after the anticoagulant effect

of the heparin is no longer apparent in the circulating blood.

EXPERIMENTAL USE OF HEPARIN PELLETS

An experiment was undertaken to determine what effect, if any, the local use of heparin had on the development of postoperative fibrosis and filtration in the normal rabbit eye following a filtering operation.

Heparin pellets manufactured and stored as described above were used throughout. Albino rabbits were shaved closely about the lids with an electric clipper and were anesthetized with 300 mg. of nembutal per kilogram of weight by the intravenous route. The skin of the lids was painted with 3.5-percent iodine. Pontocaine was instilled into the conjunctival sac and, under sterile conditions, an iris inclusion operation was performed through a keratome incision. A large flap of conjunctiva extending well back to the equator was employed in each case. The optimal site for such a procedure was found to be the superior portion of the globe next to the lateral muscle. A fine running silk suture was used to close the flaps. In some cases, the sphincter of the iris was cut; in others, the iris was included without cutting.

In those eyes in which heparin implants were used, a milligram of heparin in 0.1 cc. solution was introduced into the anterior chamber as soon as the keratome incision was made. A heparin pellet was then placed at the site of the inclusion or right adjacent to it and the flap was closed (fig. 3). Sutures were removed during the second week under topical pontocaine.

The eyes operated upon fall into three groups: (1) Those in which heparin was implanted directly; (2) those in which no heparin was implanted and where the animal received no heparin; and (3) those in which no heparin was used directly, but where a heparin pellet had been placed under the conjunctival flap in the opposite eye within a half hour. In this way we were able to observe the effect of varying uncontrolled degrees of systemic heparinization and in-

Fig. 4 (Bick and Haines). Appearance of rabbit eye prior to injection of trypan blue.

Fig. 5 (Bick and Haines). When the dye was confined to the bleb, filtration was considered to be poor.

tense, well-controlled local heparinization.

The weight of the heparin implant employed varied from 60 to 34 mg. and averaged about 45 mg. The average weight of the rabbits employed was 2.5 kilograms. The smallest dose used was sufficient to have some effect on the clotting time for 5 hours and the largest for 18 hours. Every pellet used exceeded the tissue saturation level.

The animals were observed for 6 weeks to 2 months and, after the eyes had whitened completely, the sizes of the blebs were compared, and filtration was observed.

Filtration was estimated by puncturing the cornea with a hypodermic needle, allowing most of the aqueous to escape, and then injecting 0.1 cc. of 1-percent solution of trypan blue. The rapidity of filling of the conjunctival bleb, the amount of filling, and the spread of the dye under the conjunctiva were observed for 15 minutes.

Filtration was classified in three groups: (1) Absent, (2) poor, or (3) good. If the bleb filled slowly and incompletely during the period of observation, the filtration was considered to be poor (figs. 4 and 5). If the bleb filled rapidly and the dye spread out under the conjunctiva around the bleb, filtration was considered to be good (fig. 6). The

size of the bleb in general corresponded to the degree of filtration present. There were exceptions, however, and grading was made solely on the basis of the spread of the dye.

After the filtration experiment, the rabbit was killed, and the eyes were fixed in Zenker's solution for histologic study.

RESULTS

The results of the filtration experiments in the three groups are summarized in Table 1.

If the absent and poor filtration are
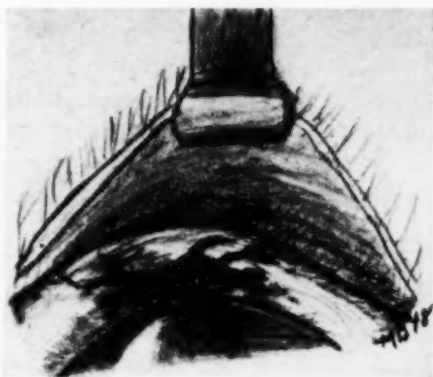
Fig. 6 (Bick and Haines). When the dye spread under the conjunctiva outside the bleb, filtration was graded as good.
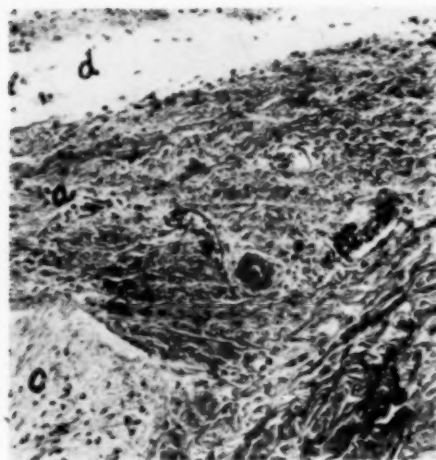
Fig. 7 (Bick and Haines). Section taken from the control eye in which no filtration was observed. The heavy episcleral layer of fibroblasts (a) arising from normal sclera (b) which bridges over the iris (c) impeded the spread of trypan blue to the subconjunctival space (d).

grouped together, a statistically significant difference exists between Groups 1 and 3 which gives $x^2 = 5.49$.

Since $P = 2$ at 5.412, there are only 2 chances in 100 that the observations are a matter of chance.

The differences observed indicate that intense local heparinization with saturation of the tissues is of benefit in promoting filtration.

HISTOLOGIC OBSERVATIONS

In a correlation of the histologic picture with the degree of filtration recorded on our

test, one is impressed that there are two critical points which determine the success or failure of filtration. These are: (1) The channels from the anterior chamber between the iris and the cornea on one side and sclera on the other, and (2) the organization and thickness of the fibroblastic layer overlying the iris under the conjunctiva. This fibrous layer bridges the iris from the cornea to the sclera.

In Figure 7, the normal sclera is seen in the lower right corner. The iris is in the lower left corner and, above this, is the very heavy layer of fibroblasts which bridges over the iris. Overlying this is the subconjunctival tissue. This heavy fibrous capsule impeded the spread of trypan blue so that no filtration was possible. This section was taken from one of the control eyes in which no filtration was observed.

In Figure 8, the channel between anterior chamber and subconjunctival space is closed by organization of the iris with episcleral fibrous tissue so that a free channel from the anterior chamber does not exist. Even though the iris is well incarcerated and the fibrous subconjunctival layer is not excessively thick, no filtration was observed.

TABLE 1

FUNCTION OF FILTERING OPERATIONS IN
HEPARINIZED AND NONHEPARINIZED
RABBIT EYES

Filtration	Group 1 Heparin Implant (Locally)	Group 2 Heparinized (Remotely)	Group 3 Control
Absent	0	2	3
Poor	10	7	8
Good	7	4	1
	17	13	12
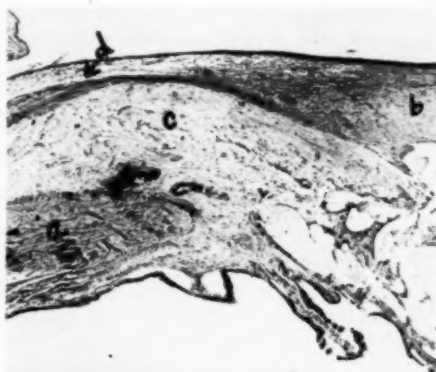
Fig. 8 (Bick and Haines). Section from control eye in which no filtration was observed. There is no free channel from the anterior chamber. The episcleral fibrous layer is not excessively dense. (a) Sclera, (b) cornea, (c) iris, (d) episcleral fibrous layer.

In Figure 9, taken from one of the eyes in which a heparin pellet was directly placed, we observe a free channel over the anterior but not the posterior surface of the iris. The fibrous layer extending from the episcleral tissue is of sufficient thickness to impede filtration. Filtration was rated as poor in this eye.

In Figure 10 one is able to see a free channel of flow from the anterior chamber. The fibrous layer is loosely organized and allows the formation of cystic spaces. Both of these sections represent eyes in which filtration was rated as good, and in which heparin implants were placed at the time of surgery.

DISCUSSION AND CONCLUSIONS

A heparin pellet dissolves somewhat more rapidly in the aqueous than under the conjunctiva. The high solubility of heparin in tissue fluids and its relatively slow appearance in the blood stream indicate that it remains locally in high concentrations even though the pellet has dissolved. This would seem to fit in with the known facts that heparin is nondialyzable and forms dissociable complexes with proteins.[2] We were able to follow the release of heparin into the

Fig. 9 (Bick and Haines). Filtration was rated poor. Despite a free channel over the anterior surface of the iris, a dense episcleral layer of fibrous tissue impeded filtration to the subconjunctival space. (a) Cornea, (b) sclera, (c) iris, (d) episcleral fibrous layer.

blood stream for almost 24 hours following local implantation. A pellet of 30 mg. is sufficient to saturate an implantation site and have a slight excess detectable in the blood stream of the rabbit.

How long heparin remains effective locally is still to be determined. From the present study, it would appear that heparin remains for a sufficient period of time locally to
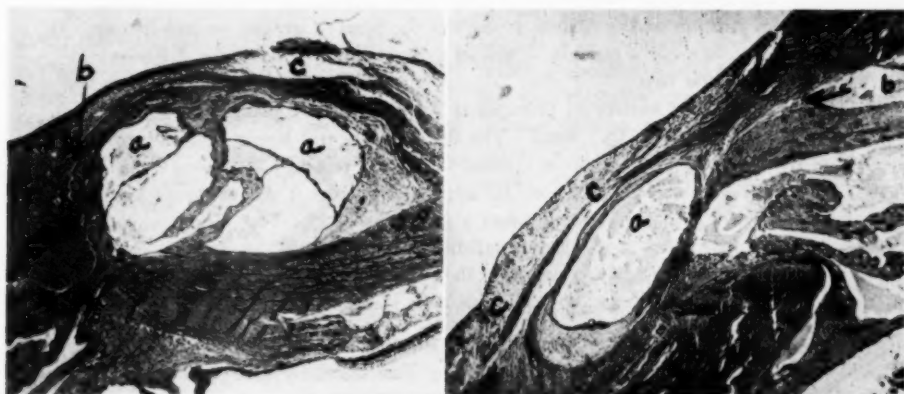
Fig. 10 (Bick and Haines). Sections taken from eyes in which heparin implants were used. The episcleral fibrous layer is loosely organized and permits the formation of cystic spaces (a). There are open channels between the anterior chamber (b) and the subconjunctival space (c).

modify in some manner the normal process of tissue repair. There is enough heparin present to prevent fibrin formation for at least a day, and this may be all that is required to improve filtration in the normal rabbit eye.

Heparin pellets implanted at the site of filtering operations caused no undue reaction and histologic observations made during the first week after subconjunctival implantation substantiated this gross observation.

There is no reason why heparin cannot be used locally in the human being in the same manner as in the rabbit. A pellet of 30 to 60 mg. should have little or no effect on the blood coagulation time in the human. On theoretical and experimental grounds, such implantation of heparin might be of value in those cases where fibrin formation and secondary fibrosis are to be avoided. It should be borne in mind that the eyes used in our animal study were not inflamed or congested, conditions where heparin might show its full usefulness.

SUMMARY

The preparation of heparin pellets was briefly described. The local absorption of heparin pellets placed in ocular tissues was observed. The experimental use of heparin pellets at a filtering site indicates that intense local heparinization is of benefit in promoting filtration in the normal rabbit eye.

Heparin causes no undue local reaction.
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OPHTHALMIC MINIATURE

There are four varieties of protuberance of the iris. The first, resulting from rupture of the cornea, resembles the head of an ant, so that it may be mistaken for a pustule. I will in a short time speak of the difference between the two.

The second variety of prolapse is larger and more prominent than the first. It is called "fly's head." The third sort is still larger and may protrude so far as to come in contact with the eyelashes. This condition is a very serious bar to vision. Its appearance gives it the (vulgar) name of "berry," and it certainly has a grapelike shape. The fourth variety bears the vernacular name "nail-head." It is found in chronic cases, where the cornea has grown over the protrusion, thus giving the swelling the likeness attributed to it. Paulus calls it simply "finger nail."

Memorandum Book of a Tenth Century Oculist
Translated by Casey A. Wood.

THE EFFECT OF RETROBULBAR ALCOHOL INJECTION ON THE EYES OF EXPERIMENTAL ANIMALS*

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In the course of the study on the physio-pathology of experimental corneal grafts in conjunction with Maumenee, it was found that all auto- and homografts inserted into a cornea made insensitive by a retrobulbar injection of alcohol prior to the operation either became cloudy, infected, or sloughed. The details of these findings will be recorded elsewhere. It suffices to note that 14 out of 14 grafts (100 percent) were total failures if 0.25 cc. of 95-percent ethyl alcohol was injected into the orbits of rabbits, 6 days, 9 days, 10 days, 11 days, 20 days, and 42 days before operation. This is in sharp contrast to the average percentage of successful homografts into clear corneas which, in our series, amounts to approximately 75 percent.[1]

The clarity of the graft did not seem to be appreciably influenced by performing the following procedures before operation: (1) Cutting the corneal nerves by an incision down to Descemet's membrane around the entire periphery of the cornea, thereby causing insensitivity of the cornea; (2) removal of both the Harderian and lacrimal glands; (3) removal of the superior cervical ganglion, thereby severing the sympathetic innervation to the cornea. It was therefore thought that the retrobulbar injection of alcohol might cause changes in the eye different from those which were produced by the procedures mentioned above.

As the clinical use of retrobulbar alcohol injections for painful blind eyes and even for various chronic conditions in seeing eyes becomes more popular, an experimental evaluation of changes in the eye following such injection appears appropriate. Very little experimental work on retrobulbar alcohol in-

jection has been reported. The only experimental approach was made by Weekers[2] who injected 1 cc. of an 80-percent solution of ethyl alcohol into the orbit of one rabbit. The author noted the hypotonic effect of this injection on the intraocular pressure of his animal.

EXPERIMENTAL STUDIES

The experiments to be reported here consist of clinical, histologic, and chemical studies.

TECHNIQUE

The technique for retrobulbar alcohol injection in rabbits was similar to that used in man. Albino rabbits weighing around 2,500 kg. were given general anesthesia by injecting nembutal intravenously. In spite of anesthesia the corneal reflex could still be elicited. A needle (24 gauge, ¾ inch) was inserted through the conjunctiva between the external and inferior rectus muscles pointing to the apex of the orbit. As soon as the optic nerve could be felt with the needle, the syringe was drawn back for a few millimeters and 0.25 cc. of 95-percent ethyl alcohol was injected slowly into the orbit. After a successful injection the corneal reflex was abolished immediately and the pupil became dilated and fixed to light. In the majority of the cases only one eye was injected; the other eye served as control.

CLINICAL OBSERVATION

The conjunctiva in the upper nasal part usually became injected and chemotic a few hours after introducing alcohol into the orbit. The chemosis persisted for 3 to 4 days. The deeper vessels in the episclera did not seem to be dilated and the bulk of the reaction was found in the conjunctiva only. The vessels of the iris were slightly more apparent during the first few hours. After four

Fig. 1 (Kornblueth). External eye muscle of rabbit three days after retrobulbar alcohol injection showing heavy round-cell infiltration, destruction of muscle fibers, and proliferation of fibroblasts. (Histologic section. Hematoxylin-eosin stain. ×100.)

days the eye usually looked entirely normal. It was noted that, if a larger amount of alcohol (0.5 cc.) was injected, a marked enophthalmos developed later.

The cornea stayed clear indefinitely unless some lesion was caused intentionally or unintentionally. The latter happened if, by technical mistake due to leakage of the needle, a drop of alcohol fell onto the cornea: an erosion developed thereafter which healed only after a long period of time. In cases where an extreme chemosis of the conjunctiva persisted for a longer time and the animal was unable to move its lids due to the swelling of the conjunctiva, an exposure keratitis developed.

The duration of the insensibility of the cornea varied with the amount of alcohol injected; if only 0.15 cc. of 95-percent alcohol was given, a corneal reflex could not be elicited for nearly 3 weeks. If 0.25 cc. to 0.3 cc. was injected, an average of 6 to

7 weeks passed until the sensibility of the cornea returned. In a great many, if not in all cases, the pupillary reaction to light was regained as the sensibility of the cornea returned to normal.

HISTOLOGIC STUDIES

The rabbits' eyes were enucleated following the orbital injection at intervals ranging from 3 days to 3 months, in order to study the histologic changes in the coats of the eyes, the optic nerve, and the orbital tissues. Care was taken to cut as long a piece of the optic nerve as possible. Three days after the injection the most marked changes were found in the muscle which showed a heavy round-cell infiltration, destruction of the muscle fibers, and early proliferation of fibroblasts (fig. 1). The orbital fat also was
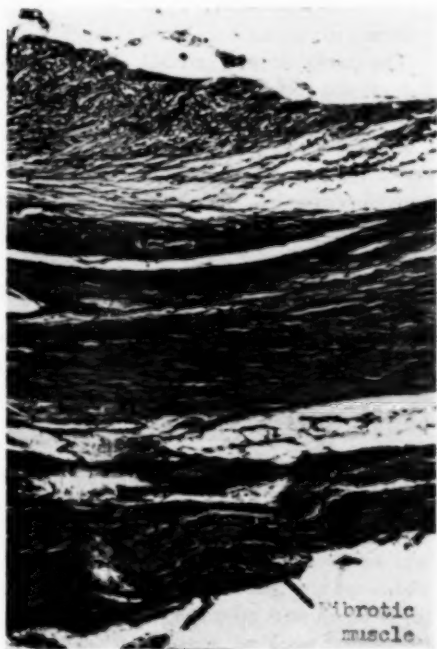
Fig. 2 (Kornblueth). External eye muscle of rabbit 57 days after retrobulbar alcohol injection showing fibrosis of the muscle fibers. (Histologic section. Hematoxylin-eosin stain. ×100.)

interspersed with lymphocytes. Neither the sclera, the optic nerve, nor its sheaths presented any sign of inflammation. Nine days after the injection the orbital tissue seemed almost normal except for proliferation of fibroblasts in the muscle which eventually led to fibrosis and adhesions to the globe (fig. 2). At no time did the optic nerve show any inflammatory reaction or signs of degeneration.

An interesting finding was observed in the corneal nerves. They were stained according to the silver impregnation method of Bielschowsky-Gros slightly modified by Campos. This method is reported in detail elsewhere.[3] Four days after the retrobulbar alcohol injection, the nerves still stained normally, but on the sixth day changes began to appear. Many nerves stained more faintly than normal, while other fibers still appeared to be normal (fig. 3). Twenty-seven days after the injection a majority of the nerves appeared pale, and at 48 days, the time when the sensitivity of the cornea started to return, most of the nerves again stained normally. At 57 days the nerves could not be differentiated from normal corneal nerves (fig. 4).

Fig. 4 (Kornblueth). Rabbit cornea 57 days after retrobulbar alcohol injection showing normally stained nerve fibers. (Histologic section. Silver impregnation. ×100.)

FACTORS IN NORMAL HEALING

The poor results obtained with corneal transplants and the slow healing of minor injuries of the cornea after retrobulbar alcohol injection suggested that the various factors in normal healing which could be quantitatively assayed should be investigated. Therefore the following experiments were performed:

Determination of mitosis rate in the corneal epithelium of rats. White rats weighing 120 to 150 gm. were anesthetized with ether and 0.04 cc. of 95-percent alcohol was injected behind the globe. A high percentage of the rats thus injected developed an exposure keratitis and had to be discarded. In the remaining rats whose corneas stayed clear, a mitosis count on corneal epithelium was done after stopping the division of the cells in metaphase by injecting colchicine (5 mg./kg.) prior to enucleation. This method was devised by Buschke, Friedenwald, and Fleischmann.[4] The mitosis count showed a loss of 30 percent 3 days after the injection of alcohol, but increased to 30 percent above normal on the 4th day, and dropped to 31 percent below normal on the

Fig. 3 (Kornblueth). Rabbit cornea six days after retrobulbar alcohol injection showing faintly stained nerve fibers. (Histologic section. Silver impregnation. ×100.)

6th day. After 14 days, the mitosis count was still 25 percent below normal and, 3 weeks following the injection, the loss amounted to 41 percent. After 5 weeks, the mitosis rate returned to practically normal (− 10 percent). See Graph 1.

Movement of epithelial cells in the healing of corneal wounds. The method of Friedenwald and Buschke[8] was used. This the whole cornea was removed by scraping with a ring curette. Drops of penicillin solution (1,000 units/cc.) were instilled daily during the period of healing. While all the control eyes showed normal and clear epithelium after 7 days, only 3 of the 11 eyes (3 days, 9 days, and 10 days after retrobulbar alcohol injection) became covered with epithelium and showed a clear surface. In
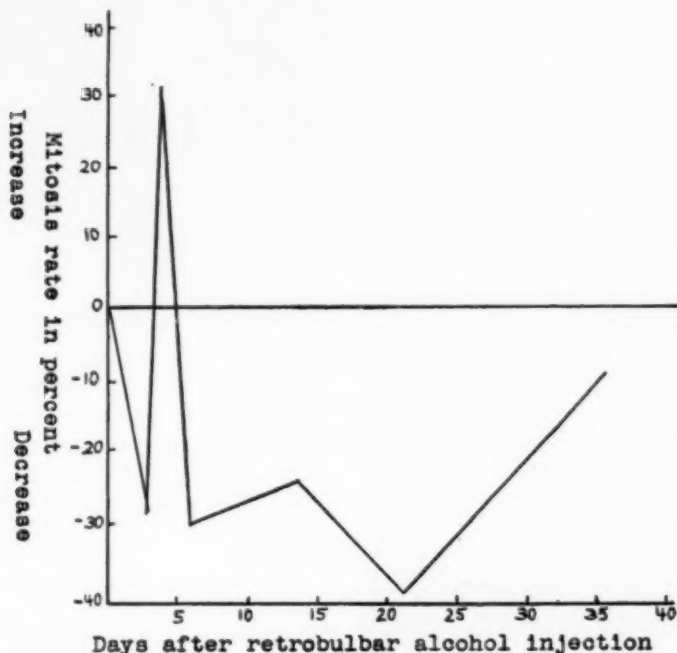
Graph 1 (Kornblueth). Mitosis rate of corneal epithelial cells of rats after retrobulbar alcohol injection. Each point on the graph represents a value of at least three eyes.

method was described as follows: "With a fine pointed needle about 30 small circular epithelial injuries are produced in the cornea of rats under ether anesthesia." The time required to fill the defect by cell movement in the retrobulbar alcohol-injected eyes compared well with the normal values.

Removal of epithelium of whole cornea of rabbits. In 11 eyes (3 days, 7 days, 9 days, 10 days, 18 days, and 19 days after retrobulbar alcohol injection) the epithelium of these 3 it took approximately 3 weeks for reëpithelization. One of the corneas which became normal showed a recovery of sensibility in the course of healing. In 8 eyes the corneal epithelium remained irregular, was loosely adherent to the stroma, and had a tendency to slough. Vascularization and occasional secondary infection were noted in these eyes.

On histologic examination of the 8 eyes just mentioned, the epithelium often com-

prised only one layer and did not show any tendency to adhere to the underlying stroma. Fibrous tissue and newly formed capillaries were observed under the epithelium (pannus degenerativus) (fig. 5). In some of the corneas, the stroma became vascularized and infiltrated with leukocytes. In order to ex-

Destruction of corneal stromal cells. In a paper reported elsewhere[6a-6b] a method for destroying corneal stromal cells in a limited area by application of solidified carbon dioxide was given, and the mode of repair of the stromal cells described. With this technique, the corneas of rabbits (3, 6, 7, 11, 12, 14,

Fig. 5 (Kornblueth). Rabbit cornea 59 days after retrobulbar alcohol injection, 41 days after scraping of epithelium of whole cornea, showing fibrous tissue beneath the regenerated epithelium. Notice the thin epithelial layer. (Histologic section. Hematoxylin-eosin stain. ×100.)
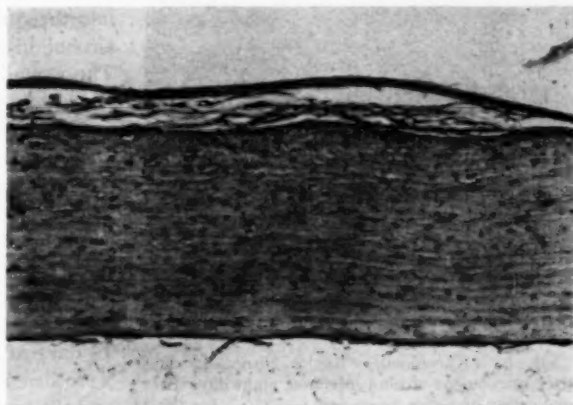
clude the possibility that a secondary infection had inhibited the reëpithelization in these large denuded areas, experiments were performed with smaller lesions.

Removal of corneal epithelium in a circumscribed area. In 3 eyes (4 days, 14 days, and 25 days after retrobulbar alcohol injection) the epithelium of the cornea was removed in an area 4.5 mm. in diameter and the course of epithelization was followed. While the control eyes did not show any stain with fluorescein after 2 to 3 days, 2 of the retrobulbar alcohol injected eyes healed only after 8 days. One of these 2 eyes became sensitive 5 days after healing; the other showed a loosening and sloughing of epithelium 8 days after the originally injured area could not be stained with fluorescein. It was again covered with epithelium 10 days later. The 3rd eye healed only after 16 days. The 2 latter eyes regained some sensitivity before epithelization was complete. Nevertheless, this did not seem to promote normal healing of the wound.

and 18 days after retrobulbar alcohol injection) were injured by freezing an area of 6 mm. for 3 seconds.

When one compares normal and retrobulbar alcohol-injected eyes injured in the above manner, one finds fewer mitosis in the stromal cells of the latter eyes during the first 3 to 4 days. While normal eyes showed an average of 4 to 5 mitosis per vertical histologic section cut at 8μ 3 days after the injury, the eyes which had received orbital alcohol injection gave an average of 2 mitosis per section. The same relation held true for the findings 4 days after the injury. The epithelium and endothelium were better developed in the control eyes.

At 6 days, the stroma at the area of injury in the control eyes was filled, although not very densely, with cells, while the eyes after retrobulbar alcohol injection showed large areas devoid of cells. These latter eyes still showed some acellular areas after 8 days, while the control eyes were filled completely with cells at that time (figs. 6a and 6b).
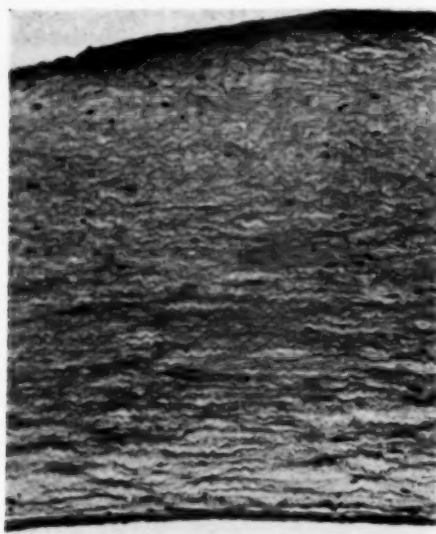
Fig. 6a (Kornblueth). Rabbit cornea 14 days after retrobulbar alcohol injection, eight days after application of 6-mm. brass rod (−78°C.) for three seconds, showing regenerated corneal stromal cells. Notice the acellular areas and the still persisting edema. (Histologic section. Hematoxylin-eosin stain. ×125.)
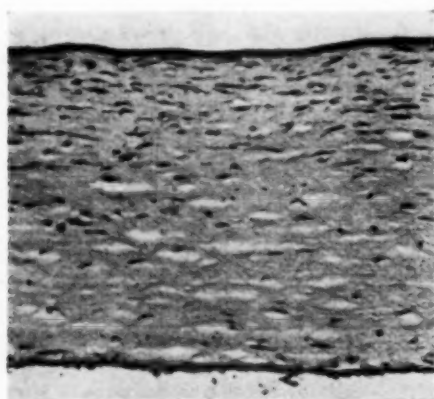
Fig. 6b (Kornblueth). Rabbit cornea eight days after application of 6-mm. brass rod (−78°C.) for three seconds, showing regenerated corneal stromal cells. Compare the density of the regenerated corneal stromal cells with those in Figure 6a. (Histologic section. Hematoxylin-eosin stain. ×125.)

Of the 5 eyes observed for 6 weeks or longer, 3 cleared up entirely after a period of 3 weeks (average normal 7 to 10 days). In 2 eyes, the edema of the stroma failed to subside. One of them also showed fibrous tissue and capillaries beneath the epithelium.

Nonperforating trephine cuts into the cornea. Nonperforating wounds were cut into the cornea 5 days after the retrobulbar alcohol injection with a 4.5-mm. trephine. The wound healed nicely, the cornea stayed clear, but the epithelium did not become firmly adherent where the trephine perforated the cornea.

Water content of cornea. In order to study whether the abolishment of the nervous control over the cornea might have some influence on the water-binding power of the cornea, the water content of this tissue was determined. Pieces of cornea (9, 10, 13, and 14 days after retrobulbar alcohol injection) were dried at 120°C. over calcium chloride and the loss of water was determined by the difference in weight before and after drying.

Although there was a slightly higher water content in the eyes following retrobulbar alcohol injections, the difference did not seem to be statistically significant.

Studies on the toxicity of aqueous in rabbits' eyes after retrobulbar alcohol injection. In order to see whether there was a toxic material in the aqueous of eyes after retrobulbar alcohol injection which inhibited wound healing in perforating wounds, the influence of the aqueous on the growth of rats' fibroblasts was studied. Pooled aqueous taken from 6 eyes, 0.2 cc. from each, from 3 days to 3 weeks following the retrobulbar alcohol injection, was added to a tissue culture of rats' fibroblasts. There seemed to be no difference in the rate of growth as compared with the normal control.

Protein determination in aqueous following retrobulbar alcohol injection. The protein content of the aqueous was determined on 0.2-cc. samples in 5 eyes from 3 days to 13 days following retrobulbar alcohol injection. The method used was the Micro-

Kjeldahl method of Markham.[7] The protein content of these samples did not exceed 10 mg. percent. This is within the lower limits of normal for the aqueous.

Vitamin C determination of aqueous following retrobulbar alcohol injection. Aqueous (0.2 cc.) was withdrawn from 9 rabbit eyes from 3 days to 23 days following retrobulbar alcohol injection and the ascorbic-acid content was determined according to the

for the tissues of the eye by Friedenwald and Becker.[10]

The glucuronidase activity in the ciliary body in 7 eyes, 4 days to 29 days following the retrobulbar alcohol injection, was examined. During the first 4 days the activity remained normal, but increased 18 percent on the 5th day and fell to 10 percent above normal on the 9th day, to normal on the 24th day, and showed a loss of 30 percent activity
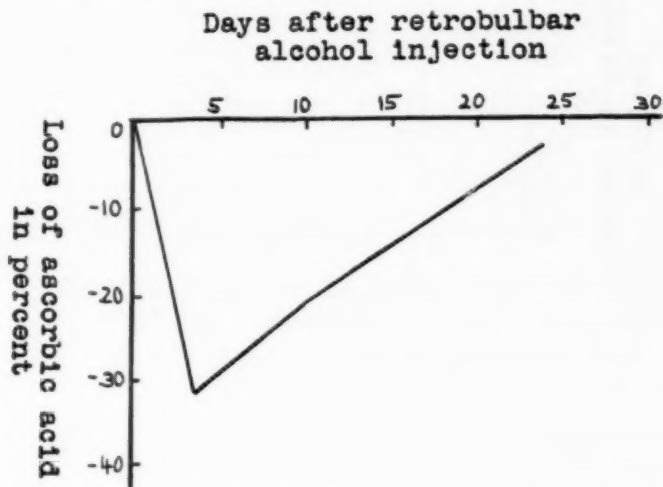
Graph 2 (Kornblueth). Ascorbic-acid content of aqueous of rabbits after retrobulbar alcohol injection.

method of Birch, Harris, and Ray as modified by Buschke.[8] The results are given in Graph 2. Three days after the injection there was a loss of 30 percent of vitamin C in the aqueous which recovered to 21 percent loss at 9 days and returned to normal after 23 days.

Determination of glucuronidase in the ciliary body. The next step was to examine one of the enzymatic activities of the ciliary body. A method has been described by Tahaly, Fishman, and Huggins[9] for the quantitative determination of glucuronidase, an enzyme which catalyzes the hydrolysis of the glucuronide linkage. The method which was used in this study was recently adapted

on the 29th day (graph 3). A similar but sharper increase in the activity of glucuronidase was found in the lacrimal and Harderian glands during the first few days after alcohol injection. These levels fell to normal around the 26th day (graphs 4 and 5). On inspection neither the lacrimal nor Harderian glands appeared atrophic following retrobulbar alcohol injection.

Rate of flow of aqueous in rabbits' eyes following retrobulbar alcohol injection. It seemed that a clue on the secretory activity of the ciliary body could be found by determination of the rate of flow of the aqueous according to the method described by Friedenwald.[11] "Under nembutal anesthesia
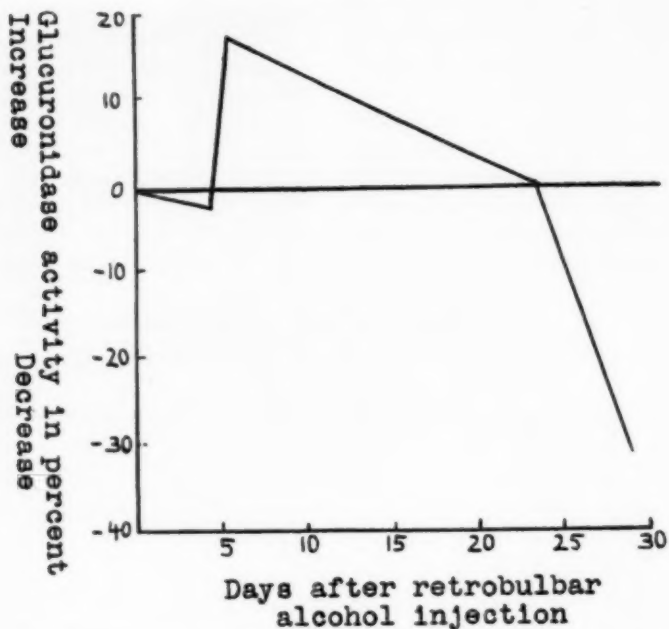
Graph 3 (Kornblueth). Glucuronidase activity in ciliary body of rabbits after retrobulbar alcohol injection.
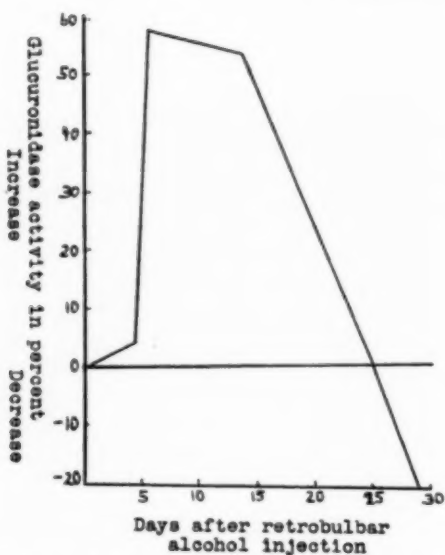
Graph 4 (Kornblueth). Glucuronidase activity in lacrimal gland of rabbits after retrobulbar alcohol injection.
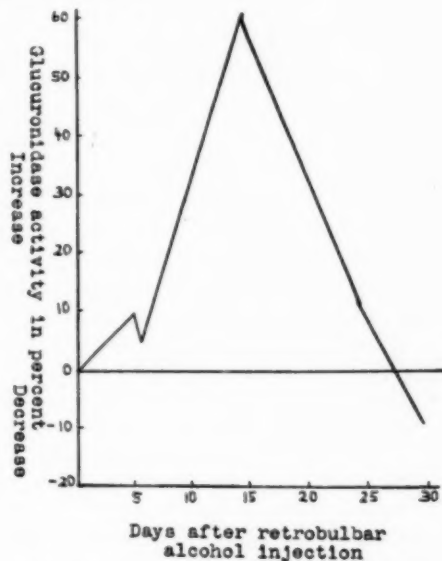
Graph 5 (Kornblueth). Glucuronidase activity in Harderian gland of rabbit after retrobulbar alcohol injection.

with local instillation of 0.5-percent ponto-
caine a compensatory manometer was con-
nected with the anterior chamber of one eye
of a rabbit. As soon as the pressure reached
a stable equilibrium 0.143 cc. of aqueous was
withdrawn and the subsequent course of the
intraocular pressure observed."

In untreated animals the intraocular pres-
sure returned to normal after 5 minutes
(graph 6a), while in one animal (3 days
after retrobulbar alcohol injection) the
tension came back only after 10 minutes
(graph 6b), and in a 2nd animal (3 days
after retrobulbar alcohol injection) the eye
did not reach its original tension even after
25 minutes.

*Tension curves of eyes after retrobulbar
alcohol injection.* The hypotonic effect of a
retrobulbar alcohol injection on the treated
eye and a concomitant ophthalmotonic effect

in the other untreated eye has been men-
tioned by Weekers.[12] Since Weekers used a
relatively large amount of alcohol (1 cc. of
80 percent) in his rabbit, it seemed impor-
tant to see how a small amount of alcohol
injected into the orbit would influence the
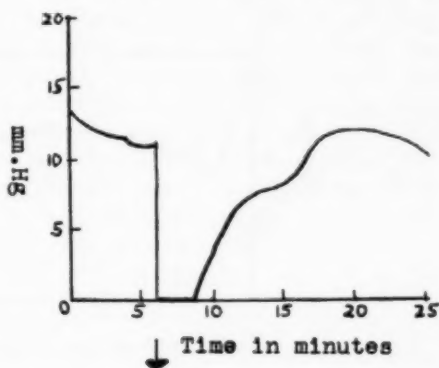
Graph 6b (Kornblueth). Rate of flow of aqueous
in rabbit three days after retrobulbar alcohol in-
jection. ↓ —0.143 cc. of aqueous withdrawn.

tension in the treated as well as in the fellow
eye.

A series of 10 animals were given a retro-
bulbar alcohol injection of 0.25 cc. of 95-
percent alcohol on one side. The ocular ten-
sion was compared in the normal and treated
eye. The tension was measured with a
Schiøtz tonometer. It is realized that the
curvature of the rabbit's cornea varies from
the curvature of the human cornea and the
foot plate of the tonometer does not, there-
fore, fit. However, the measurements give a
comparative value. The tension dropped
sharply one day after the injection and re-
covered slowly to normal after 14 to 20 days.
The typical change in the ocular tension after
treatment is presented in Graph 7. No lower-
ing of tension could be observed in the un-
treated eye.

The tension was also measured in eyes in
which the orbital alcohol injection was given
on the nasal side of the muscle cone. In these
eyes the corneal sensitivity remained intact.
The eyes receiving retrobulbar alcohol in-

Graph 6a (Kornblueth). Rate of flow of aqueous
in normal rabbit. ↓ —0.143 cc. of aqueous with-
drawn.

jections in the nasal side of the muscle cone showed an external inflammatory reaction similar to that found in eyes for which the injection was made in the region of the ciliary ganglion. However, the drop in ocular tension was not as marked and was only

rabbits, which have just been described, are probably similar to those in man following such injections. The amount of alcohol chosen for injection into the orbit of rabbits, 0.25 cc. of 95-percent alcohol, compares well with that given clinically to humans, 1 cc.
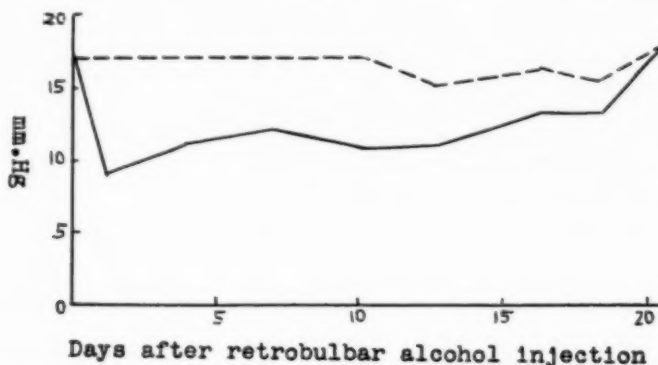
Graph 7 (Kornblueth). Tension curve of rabbit eye after alcohol injection into right orbit. R.E.: ———; L.E.: ----.

transitory. It took 3 to 5 days for the ocular tension to return to its original level (graph 8).

DISCUSSION

The reactions in the eyes and orbits, following retrobulbar alcohol injections in
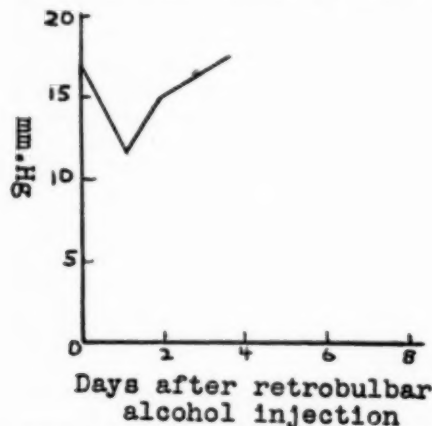
Graph 8 (Kornblueth). Tension curve of rabbit eye after retrobulbar alcohol injection into the orbit without interrupting the nervous supply to the eye.

of 95-percent alcohol. The volume of the human orbit is approximately 4 times that of a 2.5 to 3 kg. rabbit. If, however, 1 cc. of novocaine is used prior to the retrobulbar alcohol injection, as has been described by some workers,[16] the immediate concentration of the injected alcohol is probably diluted to some extent. This dilution may eliminate some of the sclerosing effect of the more concentrated solution.

Some of the rabbits' eyes showed a slight deviation to the temporal side following retrobulbar alcohol injection. This was not due to a paralysis of the muscles but to fibrous adhesions between the external rectus muscle and the globe which formed as a result of the inflammatory reaction caused by the injection.

The healing process of trivial injuries (stippling of the cornea with a fine needle, nonperforating cuts with a trephine into the corneal stroma) did not seem to be affected by the injection. In larger injuries, however, the defect was covered by epithelium very slowly and even then the newly formed epi-

thelium did not exhibit the vitality of normal epithelium. The regenerated epithelium often comprised only one layer and did not adhere normally to the underlying stroma. Thus, large bullæ were frequently formed and a pannus degenerativus occurred as a result of the chronic irritation.

The reciprocal relation of vitamin C in the aqueous and the glucuronidase activity of the ciliary body is interesting. As the value of vitamin C of the aqueous decreases, the glucuronidase in the ciliary body increases. This, according to Friedenwald[13] might be due to the decrease of an inhibitor (ascorbic acid) rather than an active increase in glucuronidase. Friedenwald and Becker[14] have shown that ascorbic acid inhibits the enzyme in vitro.

A comparison of Graphs 7 and 8 shows a marked difference in the degree of lowering of the intraocular pressure and the duration of the decrease if the injection was given in such a way as to interrupt the nervous supply to the eye. This would suggest that the reduction in tension is not only "due to provocation of an active hyperemia first in the orbit, then indirectly in the eye" (Weekers[15]) but due to some neurogenic influence. No concomitant fall in the tension in the other noninjected eye was observed.

Although no explanation for the peculiar action of the retrobulbar alcohol injection can be given, some possible single factors may be excluded. Cutting the nerves around the entire periphery of the cornea deprived the cornea of its nervous supply and, therefore, of its sensibility. It might be argued that not all the nerves were destroyed. Even if only 90 percent of the nerves were cut (serial sections in selected cases showed a degeneration of nearly all the nerves) some effect on the clarity of corneal transplants and healing of the surgical wound should have occurred if sensibility of the cornea was a deciding factor. However, such lesions healed without complications.

It might be theorized that retrobulbar alcohol injections destroyed the function of the Harderian and lacrimal glands. However, removal of these organs before performing a keratoplasty did not affect the final clarity of the graft. The glucuronidase activity in the ciliary body remained normal after the glands had been excised.

Removal of the superior cervical ganglion before operation had no adverse effect on a graft which was inserted on a cornea thus deprived of its sympathetic supply. The glucuronidase activity of the ciliary body, Harderian and lacrimal glands showed normal values after superior cervical ganglionectomy; nor was the rate of flow of the aqueous changed as shown in a previous paper by Friedenwald.[11]

Notwithstanding the difference in behavior of the rabbit and human corneas as regards the return of sensitivity following orbital alcohol injections (the human cornea stays insensitive only for a few days, while the rabbit cornea regains sensitivity in 6 to 7 weeks), one important conclusion can be drawn. During the period of action of the alcohol injection, the tendency of corneal wounds to heal seems to be diminished in rabbits. This should serve as a warning against clinical use of retrobulbar alcohol injections in cases of chronic ulcerative processes of the cornea.

SUMMARY

The effect of retrobulbar alcohol injections in the eyes of rabbits and rats was examined. The influence of the injections on the clarity of corneal grafts, sensibility of the cornea, corneal nerves, optic nerve, orbital tissue, pupillary reaction, mitosis rate and cell migration of the epithelial cells, wound healing in regard to epithelial and stromal wounds, regeneration of corneal stromal cells, water content of the cornea, toxicity of the aqueous, protein and vitamin-C content of the aqueous, glucuronidase activity of the ciliary body, Harderian and lacrimal glands, rate of flow of the aqueous, and ocular tension was studied.

The action of the retrobulbar alcohol in-

jection could not be explained, but neither cutting the corneal nerves around the entire periphery of the cornea, nor removal of the lacrimal and Harderian glands, nor extirpation of the superior cervical ganglion showed an effect on the eye equivalent to the one of retrobulbar alcohol injection.

A marked inhibition in wound healing in larger injuries of the cornea was observed. The conclusion was therefore drawn that the clinical use of retrobulbar alcohol injections in cases of chronic ulceration of the cornea might be detrimental to the process of wound healing.

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HISTOPATHOLOGY OF INTERSTITIAL KERATITIS
DUE TO CONGENITAL SYPHILIS*

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For the last 20 years, excepting the one case of Malinin-Scharkowsky[1] no reports on the histopathology of interstitial keratitis of congenital syphilitic origin have been recorded. The case of these authors refers to a girl, 12 years of age, with parenchymatous keratitis and congenital lues, whose left eye was enucleated after a severe trauma. The histopathologic picture was that of deep hemorrhagic proliferative interstitial keratitis and iritis.

The few previous cases we found in the literature refer almost all to interstitial keratitis of several months' duration. Stanculéano[2] studied the cornea of a patient with pulmonary tuberculosis. The patient had an old ulcus internum in both eyes, with destruction of the deep layers, while the superficial layers were only slightly altered. Watanabe[3] enucleated, on the patient's request, one eye that was blind due to interstitial keratitis which had appeared 7 months before.

Jaeger[4] could study the histologic appearance of the cornea in a case of keratitis with a clinical course of five months; the patient had died of hemorrhagic encephalitis. Elschnig[5] is the only one who made the histologic study of a more recent keratitis. That was the case of a girl, eight years of age. The interstitial keratitis had developed two months previously in one eye, and three weeks before examination in the fellow eye.

Stock[6] studied one eye of a 5-year-old boy, idiotic, with saddle nose and Hutchinson's teeth, who had been blind since infancy, following interstitial keratitis. Igersheimer's case,[7] described by Kunze, dealt with an old keratitis which relapsed shortly

before the patient died. There was a small necrotic focus in the parenchyma; and the lesions in the endothelium were not very marked.

Since interstitial keratitis is an inflammatory process of the cornea, which usually subsides leaving more or less satisfactory vision, one cannot enucleate the eye for the sake of histologic study only. This explains the difficulty in obtaining enough material for histopathologic examination of the different stages of the disease. This reason influenced us to take biopsy specimens from the cornea.

Keratectomies were performed in very different stages of the disease, varying from 25 days to several months after onset of the keratitis. Keratectomy is obviously an incomplete method, since it does not permit the cornea to be analyzed in its total thickness, especially in its deeper layers. This method, however, allows one to obtain better knowledge of the changes taking place in the anterior layers and in the epithelium. Since the whole parenchyma has the same structure throughout and the same source of nutrition, however, there is no biologic reason to suppose that the changes of the deeper layers should be different from those of the upper rows. By means of keratectomy or laminectomy we can gather material enough for our study and compare the histologic appearance of the corneas of different patients in the same stage of the disease. We started to make biopsy keratectomies on different corneal diseases many years ago.

The cases herein reported are of patients with congenital lues in whom the diagnosis of interstitial keratitis was confirmed. We performed 7 keratectomies in 5 patients. Treponema pallidum was searched for by Jahnel's method, but could never be found. For histologic examination the sections were

fixed in formaldehyde or Bouin's solution (twice in Ruffini's), imbedded in paraffin, and stained by routine methods (hematoxylin-eosin, trichromic, methanil yellow, and so forth).

CASE REPORTS

CASE 1

Irene B., aged 18 years, came to our clinic in early August, complaining of troubles that appeared two months previously in her left eye.

seen, especially among the cells of the basement layer.

Bowman's membrane. Bowman's membrane was normal in its whole length, keeping its homogeneous appearance. It followed a wavy course at certain portions, according to the various thickenings of the epithelium.

Parenchyma. The stroma beneath Bowman's membrane was formed by fascicles of sharply demarcated fibrils, enhanced by interstitial edema. Between the fascicles lymphocytes and proliferated parenchymatous cells were found.
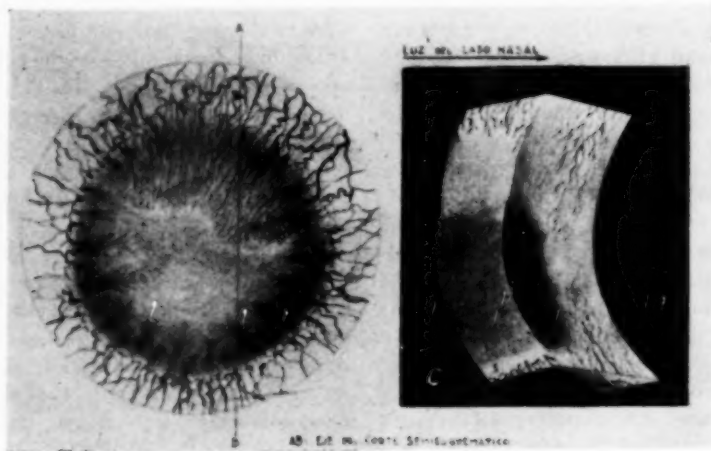
Fig. 1 (Weskamp). *Case 1.* (A-B) Gross appearance of the lesion. (C) Semischematic optic section of the damaged cornea of the left eye.

Her parents were syphilitic. The patient showed positive Wassermann and Kahn reactions (3 plus). On ocular examination we found the clinical characteristics of interstitial keratitis in full infiltrative stage. The cornea was infiltrated almost totally, mainly in its deeper layers. In the upper portions of the anterior layers a slight bedewing was seen at several points. Vascular loops were very abundant (fig. 1).

Histologic examination. Keratectomy of the left eye, external upper sector, was performed. This specimen for biopsy was taken on September 11, 1942, about 3 months after the onset of the inflammatory process in that eye.

Epithelium. Four to five layers were counted. It appeared of uneven thickness, for the cells were flattened at certain points and swollen at others. In some places the basal cells were smaller than those of the middle layers.

In general, the epithelial cells were pale, their nuclei deformed, with the chromatic network difficult to detect. Some nuclei were surrounded by a halo of perinuclear edema. Some lymphocytes were

CASE 2

This case involves the right eye of the same patient as in Case 1. While the patient was under observation for the disease of her left eye, slight photophobia and very slight perilimbic vascularity appeared in her right eye.

On slitlamp examination a small portion of the deeper layers of the upper outer segment showed a very thin infiltrate formed by minute gray dots. Little by little the infiltrate extended until it covered almost the whole upper outer quadrant. It did not extend to the pupillary border, however. At the same time, in the lower section of the cornea, very near the limbus, a spot similar to that of the upper sector appeared; it lay in the deeper layers of the cornea.

Three weeks after onset of this process the bedewing appeared on the superficial layers of the cornea, on both the upper and the lower half. The central portion of the cornea was still transparent. The perilimbic vascularity, which had been very slight at the beginning, increased as it reached

the upper half of the cornea, but it did not penetrate the stroma at any point (fig. 2).

Histologic examination. Keratectomy of the right eye, involving a piece of adjoining conjunctiva, was performed 25 days after the onset of the symptoms.

Epithelium. It appeared of varying thickness, its

were elongated in the horizontal axis. This was especially noted in the basal cells (fig. 3).

The area next to the corneoscleral limbus, which seemed to be the most seriously altered, showed the epithelial cells not in layers but in disorderly arrangement. The infiltrative elements had altered the orderly arrangement of the normal epithelium.
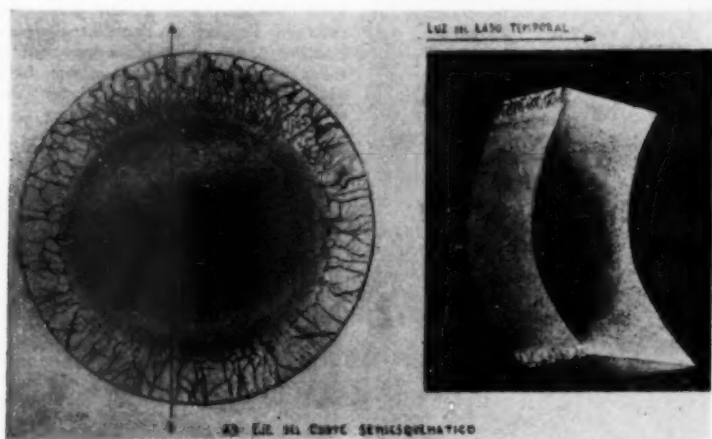
Fig. 2 (Weskamp). *Case 2.* Right eye of the same patient as in Case 1 (fig. 1).
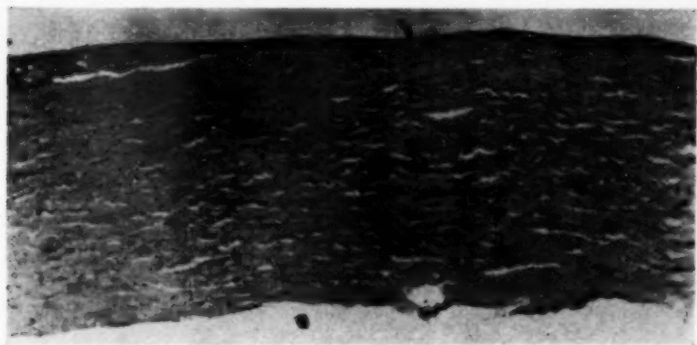
Fig. 3. (Weskamp). The varying thickness of the epithelium and the decrease of the cellular infiltrate at the parenchyma are observed.

thicker portions being at the periphery of the cornea. Here the number of invading cells was increased and an interstitial edema which formed microvesicles was present. As the infiltrative process thinned toward the center of the cornea, the epithelium also became thinner because the proper cells flattened and their number diminished. At some places the epithelium was extremely thin, only 1 or 2 rows of very flattened cells being counted. They were so flattened that their nuclei

The nuclei of the scattered epithelial cells stained well, but their cytoplasm was pale and it was difficult to outline each epithelial cell. Hematocytes, sometimes isolated, sometimes in groups or on the way to form a channel, were mingled with the flattened epithelial cells. Lymphocytes were encountered, too (figs. 4 and 5). It was difficult to identify the basal cells because they were out of place and had lost their shape.

At the central area of the cornea the epithelium

regained its orderly arrangement and the cells were distinctly outlined. The basal cells had their nuclei surrounded by a halo of intracellular edema.

Bowman's membrane appeared intact throughout: in several places it was detached from the epithelium by vesicles containing cellular elements, principally hematocytes and lymphocytes. This detachment was very marked at certain parts, as if it followed a cleavage plane. The presence of lymphocytes and red blood cells proved that the

the stained sections are actually the layers of half the thickness of the cornea.

Approaching the center of the cornea from the infiltrative focus, the infiltrative elements became scantier. The deeper layers were less invaded and their reaction was less marked. The stroma was formed by broad lamellae, as if their fibers were swollen and slightly wavy. The nuclei of the fixed cells were well stained: some of them were enlarged. Between the lamellae a hematocyte or a lymphocyte was observed. In areas still farther from the lesion, the tissular reaction consisted of swelling of the lamellar fibers and thickening of the nuclei of the fixed cells (fig. 4).

Fig. 4 (Weskamp). Epithelium disorganized and infiltrated. Adjacent to Bowman's membrane is a cyst containing hematocytes and lymphocytes. The lamellae of the parenchyma are formed by swollen fibers. Clear spaces of interstitial edema are present.

Fig. 5 (Weskamp). The very thin epithelium is formed by two layers. The parenchyma is edematous, the lamellae being formed by swollen fibers.

detachment was not an artefact. In other sites Bowman's membrane widened and merged with the underlying stroma.

Parenchyma. It was invaded by the same cells which invaded the epithelium. They were more numerous at the superficial layers. Here the lamellae formed thin fascicles with serrated borders and microvesicles of interstitial edema. Between the fascicles, hematocytes, lymphocytes, a few swollen fixed cells, and cellular detritus were encountered. At this point, the deeper the layers, the more they resembled the normal tissue, but the lamellae seemed to be formed by swollen fibers, and the lymph spaces were enlarged by interstitial edema. We must keep in mind that the deeper layers of

The histopathologic changes just described corresponded to the "dusted" appearance which was evident on slitlamp examination. As shown in Figure 2, at the optic section the bedewing extended through the superficial and through the deeper layers of the cornea, but the middle layers were normal or only slightly altered. In other words, in optic section the lesion was shaped like a great "V" with its vertex at the limbus and its opening toward the center of the cornea.

CASE 3

Zunilda Raquel C., a girl, aged 9 years, had had interstitial keratitis for three months prior to our examination. Wassermann and Kahn reactions were positive (3 plus). Biomicroscopic examination revealed an infiltrative process of the

posterior layers, but there was also haziness in the anterior layers.

Histologic examination. Keratectomy of right cornea was performed on September 4, 1942.

Epithelium. The epithelium was of varying thickness due to edema of the basal layers. This edema was mainly intracellular. The cells in general were not ruptured. The edema reminded one of Leloir's degenerative cavitary condition. This condition has been encountered in various diseases of the skin, in secondary syphilis for instance. Sometimes it has been observed as occurring technically. Several nuclei were shrunken and hyperchromic.

Small foci, formed by rests of Bowman's membrane and migratory nuclei, were seen between the epithelium and Bowman's membrane. The overlying epithelium was raised and the neighboring epithelial cells presented cariocytoplasmic changes (vacuolation, alteration of staining conditions, pyknosis, cariolysis, and so forth). In other sections the same area appeared as a cavity within Bowman's membrane and contained cellular debris and infiltrative fluid.

Bowman's membrane was present throughout and its staining propert'es were normal, but its thickness was not even and its anterior and posterior borders were serrated. In places it looked as if Bowman's membrane was fused with the underlying stroma.

Parenchyma. In general, its lamellar appearance was greatly altered. The deeper layers had lost their normal appearance and looked almost homogeneous, as if the lamellae had swollen and merged; it was difficult to outline them. The superficial layers adjoining Bowman's membrane, presented in some areas their fibrillar appearance. The parenchymatous cells were scarce and pale (fig. 6).

Fig. 6 (Weskamp). *Case 3.* Intracellular edema of the epithelium. Bowman's membrane is of varying thickness, and the appearance of the parenchymal lamellae is very altered.

CASE 4

Angela A., aged 40 years, complained of interstitial keratitis which had appeared 4 or 5 months
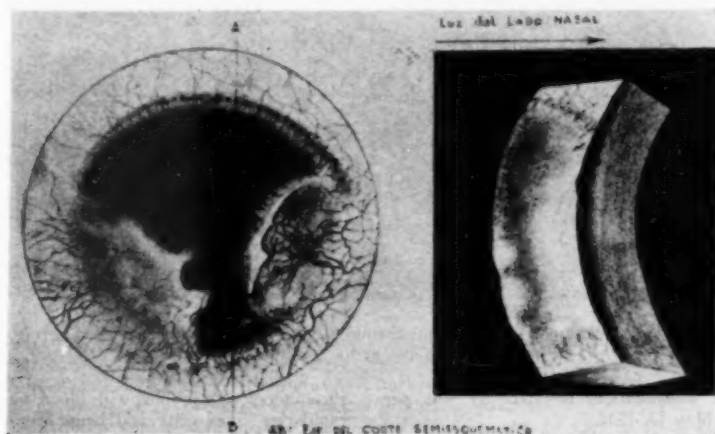
Fig. 7 (Weskamp). *Case 4.* The lesion, in the left eye, was most marked at the outer and middle layers of the cornea. There was rich vascularization with active circulation of blood.

before. Wassermann, Kahn, and Chediak reactions were positive (3 plus). She came to our clinic in April, 1942, showing a lesion in her left eye (fig. 7). In optic section we saw that the lesion was most marked at the outer and middle layers of the cornea. Rich vascularization with active blood circulation was noted.

remained normal. At the basal layer the nuclei of some cells were displaced by intracellular edema.

Bowman's membrane had disappeared.

Parenchyma. Areas were found where the parenchyma was sclerosed; in other regions it presented edema. The parenchyma was formed by thin trabeculae with wide meshes. Between these one
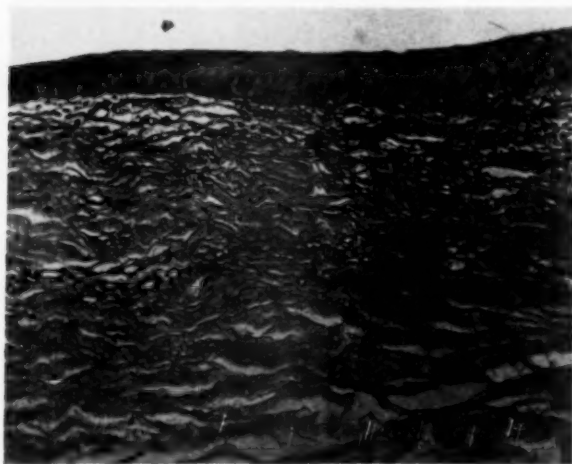
Fig. 8 (Weskamp). Broad meshes beneath the epithelium. Lymphocytes and capillaries are interspersed.
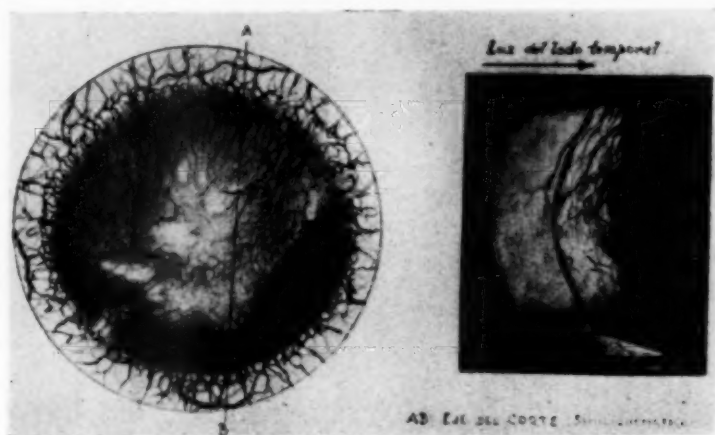
Fig. 9 (Weskamp). *Case 5.* Semischematic optic section of the damaged cornea of the right eye and the gross appearance of the lesion.

Histologic examination. Keratectomy was performed on May 13, 1942.

Epithelium was formed by 4 to 8 layers. Its inferior border was wavy; at certain points it formed a sort of papilla. It lay directly upon the parenchyma. The epithelial cells seemed to have

encountered vessels filled with blood, newly formed capillaries, fixed cells, and lymphocytic infiltrates. The lymphocytes surrounded the vessels (fig. 8).

CASE 5

Raul T., a boy, aged 20 years, showed inter-

stitial keratitis on his right eye. The lesion involved the cornea almost totally and throughout its thickness (fig. 9). The disease was of 6 to 7 months' duration. Wassermann, Kahn, and Chediak reactions were positive.

Histologic examination. A biopsy section of the cornea was taken on December 24, 1942, fixed in Ruffini's solution, and embedded in paraffin.

Epithelium. The epithelium was almost normal and its layers were in normal orderly arrangement. Interstitial edema was present in certain areas and intercellular bridges were visible. The

Between the fibers and the capillaries, fixed cells and lymphocytes were observed but, as the limbus was approached, the infiltrate became denser. This infiltrate was formed by histiocytes, lymphocytes, fixed cells, and a few polyblasts. Areas were seen in which the parenchyma was replaced by the infiltrate, mainly at the vicinity of the epithelium. In other regions very fine fibers of the stroma wove a fine network between the cells.

Vascularization in general was more marked at the subepithelial zone and through the superficial layers. The deeper layers of the biopsy presented
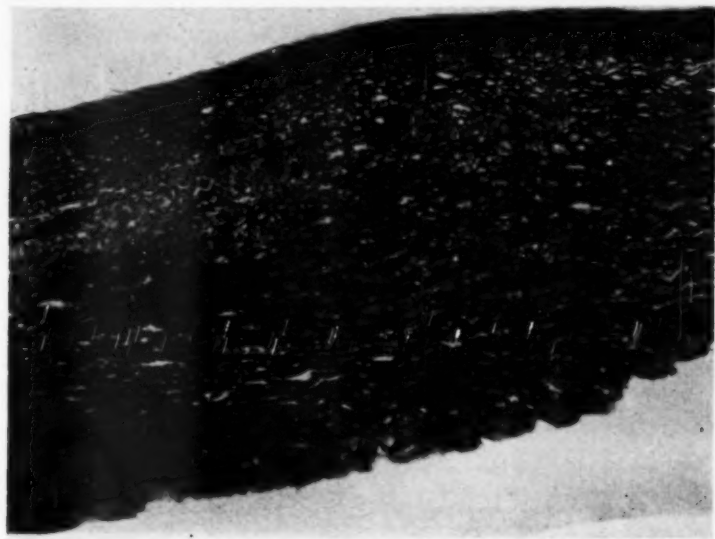
Fig. 10 (Weskamp). Bowman's membrane appears very thin. Immediately beneath it, the lamellar tissue has been replaced by bundles of fibers among which vessels and cellular infiltrates are seen.

border of the basal layer presented a slightly wavy contour but did not form papillae.

Bowman's membrane. In most places had disappeared, although the area next to the limbus remained and presented its normal appearance. It became thinner as it approached the conjunctiva, looking sometimes like a vitreous membrane. It would not have been possible to delimitate conjunctiva from cornea if one had had to follow the contour of Bowman's membrane only (fig. 10).

Parenchyma. The subepithelial stroma and the underlying layers were formed by bundles of wavy fibers which ran parallel to the surface. Between these fibers capillaries were observed that had proper walls, tumescent endothelium and the lumen totally occupied by blood elements. Most of these capillaries ran parallel with the fibers, but others had been cut crosswise and these seemed almost adherent to Bowman's membrane.

no vascularity and no infiltrate. The parenchymal lamellae were slightly tortuous and somewhat inclined to disrupt (fig. 11).

CASE 6

This case involves the left eye of same patient as in Case 5. In this eye, interstitial keratitis was 4 to 5 months old. The infiltrate was denser at the external upper and internal lower sector (fig. 12).

Histologic examination. Corneal layers of left eye were excised on December 5, 1942. The biopsy section was fixed in Ruffini's solution and imbedded in paraffin.

Epithelium was of varying thickness, 2 to 3 up to 5 to 6 rows of cells being counted. Its course was wavy and sometimes showed a wedgelike penetration of the parenchyma.

Bowman's membrane followed all the irregulari-

Fig. 11 (Weskamp). The varying thickness and irregular course of Bowman's membrane is observed. In the parenchyma, the lamellae have been replaced by bundles of wavy fibers. Vessels which have their own walls are shown.

ties of the epithelium and, at certain places, a sharp zig-zag was noted.

Parenchyma. Its normal appearance had totally changed. It was built up by a tissue of fine, sinuous fascicles intermingled like hairs on a head with numerous vessels which ran parallel to the fascicles and whose own walls were engorged.

Infiltrative elements were scattered among the interstices.

Observing the stroma with low magnification in order to obtain a panoramic view, one saw the fibrous fascicles ly'ng immediately below Bowman's membrane; but the presence of vessels was the most marked variation from the normal noted in
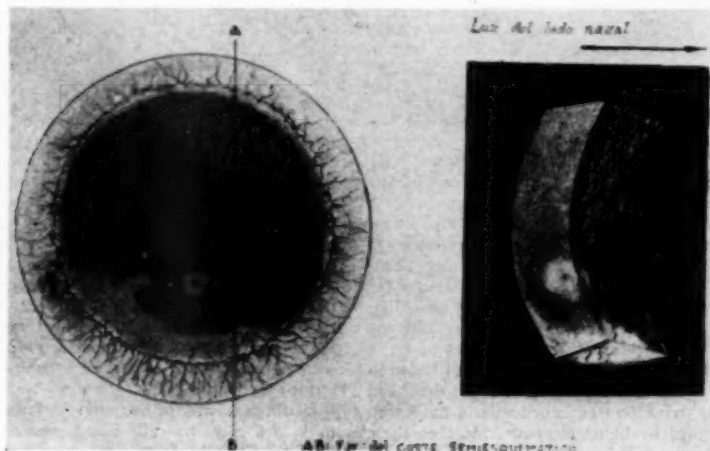
Fig. 12 (Weskamp). *Case 6.* Left eye of the same patient as in Case 5 (fig. 9).
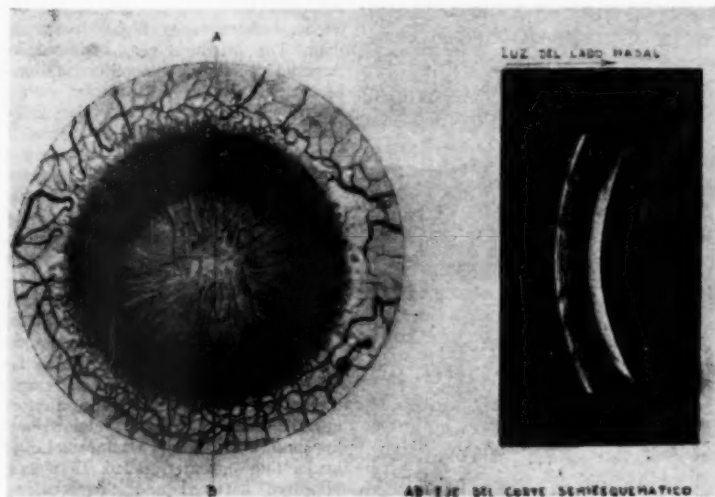
Fig. 13 (Weskamp). *Case 7*. Drawing of the left eye.
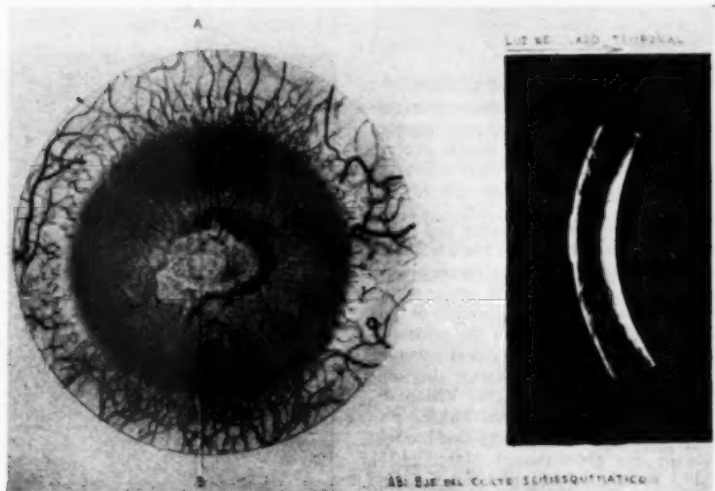
Fig. 14 (Weskamp). *Case 7*. Drawing of the right eye.

the tissue. These vessels formed a close network in the middle layers of the section. From these layers fine capillaries rose toward the upper layers. This interposed vascular network divided the parenchyma into two parts—one upper, or subepithelial, part of fine, firmly packed fibrous fascicles, among which fine capillaries were scattered; a second, lower part, situated below the vascular network. In this inferior portion the fiber fascicles were wider than on the upper part and more closely

resembled normal tissue. The middle layer, as has been said, was more vascular and exhibited many cellular elements among which were found plasmocytes, polyblasts, lymphocytes, fixed cells, and polymorphonuclear cells.

CASE 7

Juan G., a man, aged 28 years, with Hutchinson's teeth, had been given antisyphilitic treatment since childhood. His paternal uncle, a doctor, had been

occupied chiefly the posterior layers of the cornea, while at the anterior layers it was not so abundant. The middle layers appeared less changed. Arterial vessels with blood circulation were found in the deeper layers together with the whitish infiltrate. The disease was classified as residual interstitial keratitis.

Histologic examination. A biopsy of left eye was taken on March 10, 1942.

Epithelium. The structure of the epithelium seemed to remain normal (fig. 15), but its thickness was irregular, being thicker at both ends of the section where 10 rows of cells could be counted. In the center of the cornea, only 4 layers were counted. At one end the epithelium was trying to penetrate the stroma in form of a wedge. At certain regions the epithelium rested upon a repairing tissue which we shall describe later.

The epithelial cells were seemingly unaffected although they lay upon a tissue that differed from normal. Their protoplasm stained well and their appearance throughout was normal except for some nuclei that appeared faded. In places, basal cells appeared flattened and elongated, with spindle-shaped horizontal nuclei; some of these cells were so flat that they resembled thick fibers. In other parts, the row of basal cells was displaced toward the surface by a group or nest of histiocytes.

Fig 15 (Weskamp). The general structure of the epithelium remains. Bowman's membrane has disappeared in some places; in others, it appears thinner. The upper layers of the stroma are replaced by repair tissue. The inner layers are becoming normal.

the physician who administered intense and regular antiluetic treatment all through his life. Wassermann reactions at different intervals were always positive. In December, 1941, the first ocular symptoms appeared, characterized by soreness of left eye and slight decrease of vision in the same eye. An ophthalmologist diagnosed interstitial keratitis. Three months after onset of the disease the same symptoms appeared on the right eye. Vision decreased progressively to nearly total blindness in both eyes. In this condition, the patient was brought to our clinic by his physician in March, 1944, 2 years and 3 months after onset of the first symptom. The clinical appearance of the corneal lesions is illustrated in Figures 13 and 14.

Under low magnificaiton and with full front illumination the infiltrate was seen to involve almost the entire cornea, being more condensed at the pupillary area. In the right eye the infiltrate was whitish, looking like a calcareous deposit. Innumerable, glassy, radiating lines were seen in both corneas. The optic section exhibited Bowman's membrane interrupted at several points, the subepithelial tissue protruded until it reached the epithelium through those spaces where Bowman's membrane was absent. In addition, the infiltrate

Fig. 16 (Weskamp). High-power view of the section in Figure 15. The repair tissue is penetrating the epithelium. Fibroblasts are noted among the fibers. Basal cells are flattened.

Bowman's membrane. Areas were observed where Bowman's membrane (fig. 15) was absent; in other places it appeared disrupted.

Parenchyma. The anterior layers of the parenchyma were replaced by the repairing tissue already mentioned. This tissue penetrated between Bowman's membrane and the epithelium at certain regions. It was formed by thin connective fascicles running parallel to the surface. Between its interstices, stellate cells (fibroblasts) were present. It was a repairing connective tissue (fig. 16). Immediately below the epithelium this tissue showed cells very much like lymphocytes and macrophages (histiocytes). Cellular debris were also found. As the deeper layers were approached, the stellate connective cells changed into spindle-shaped; the fascicles widened; in other words, the tissue began to have the appearance of cicatricial connective tissue. Blood vessels and red blood cells were absent. Below this scar tissue, the parenchyma appeared more normal the closer one approached the deeper layers.

COMMENT

In cases of recent interstitial keratitis we observed an exudate of lymphocytes, hematocytes, and fluid (probably fibrinous) running from the limbal region through the epithelial layers and corium of the conjunctiva toward the cornea. As this exudate invades the epithelium and the parenchyma, both disintegrate and become edematous. Thus the structure and the thickness of both are altered.

The epithelium is detached from the basement membrane in long stretches, as following a cleavage plane. The detachment looks like an artefact, but the presence of red corpuscles and lymphocytes in these spaces shows that the separation is pathologic. Places are seen where edema forms vesicles containing cells with round nuclei and scanty protoplasm.

The number of epithelial layers is decreased, only 2 or 3 rows of cells are counted in places. In other spots 4 rows are seen. These cells are flattened and their nuclei lie horizontally. The basal layer does not differ from the other layers. Where the invasion is most marked, the epithelium is thicker but loses its arrangement of orderly layers, and it becomes difficult to recognize the basal cells. The epithelial cells undergo different changes. Cariocytoplasmic modifications are observed, such as perinuclear edema, hyperchromic nuclei, nuclear distortion, pyknosis, and so forth.

In advanced stages, the epithelial cells are arranged in orderly layers. The number of these is not always normal but is increased in different places. Furthermore, in cases of long-standing keratitis the basal cells have lost their characteristic features and it is difficult to distinguish them from other epithelial cells. The epithelium has a wavy contour, sometimes wedgelike, as seen in Case 6, because the structure of the parenchyma is altered, with subsequent differences of curvature of the cornea.

We have found vesicles between the epithelium and the basement membrane containing histiocytes and lymphocytes. These vesicles were also observed by Jaeger[4] in congenital luetic keratitis, and by Pieskergen (cited by Jaeger) in scrofulous keratoconjunctivitis.

Bowman's membrane is intact throughout in recent cases of luetic interstitial keratitis. In cases of longer course Bowman's membrane is disrupted when not absent in places.

Parenchyma. The intensity of the damage decreases from the surface toward the deeper layers. (One must keep in mind that the analyzed pieces were obtained by keratectomy; therefore, when speaking of "deep layers" we refer to those of the biopsy. They are not the deepest layers of the cornea, but of more or less half its thickness.) We may conclude, then, that the middle layers of the cornea are less altered. This finding is consistent with the biomicroscopic picture, where the lesions appear in the inner and in the outer layers of the cornea, leaving a less-altered middle zone.

These changes may be classified chronologically as: (1) Infiltrative and edematous stage; (2) cellular necrosis and vascularization; (3) atrophy of the parenchyma; (4) organization of fibrous tissue.

1. In recent cases of syphilitic keratitis, the parenchyma is invaded by an exudate

which comes from the limbal area carrying cells of the lymphocytic type and erythrocytes. The parenchyma is disintegrated by these infiltrates and the proper cells become swollen. The fibers appear edematous. In areas near the invaded site the parenchyma no longer appears lamellar but almost homogeneous, as if the edematous fibers were no longer demarcated. Even the nuclei of the fixed cells disappear as shown in Case 3. Here the parenchyma looks as if it had a serous inflammation.

2. After the infiltrative and edematous stage, cellular necrosis, vascularization, and invasion of macrophages follow.

3. Later on there appears atrophy of the parenchyma characterized by decrease of fixed cells and a fibrillar appearance of the corneal lamellae.

4. The most advanced stage is characterized by the organization of fibrous tissue.

The histologic structure in these different phases explains perfectly the peculiarities of the biomicroscopic appearance. In the initial phase a bedewing is observed in a sector of the cornea near the limbus. This appearance is given by an infiltrate of very small cells (red blood cells and lymphocytes) and the interstitial fluid.

As the disease progresses, the bedewing becomes condensed and gives rise to dense spots; this is due to the presence of necrotic foci and of bigger cells (histiocytes) and to the organization of capillaries.

Still more condensed areas of compact structure are observed. This picture is probably given by the presence of newly formed fibrous tissue and of vessels with active blood circulation.

CONCLUSIONS

We find that our observations are rather consistent with those of Stanculéano, Elschnig, Stock, Watanabe, and Jaeger. For an accurate comparison of the findings observed by us at the outer layers of the cornea and those observed by these authors in enucle-

ated eyes, we selected the cases of short duration reported by Elschnig and Jaeger and our own Case 1 and Case 2 which had a clinical course of 3 months and 25 days, respectively.

Epithelium. In Elschnig's case the epithelium was atrophic and was formed by the outer layer of flattened cells and a row of cubic cells. In the epithelium an infiltrate of numerous round cells was found.

In Jaeger's case the epithelium was also thinner than normal, the basal cells could no longer be distinguished from the cells of other layers. Vesicles with lymphocytes were lying between the epithelium and Bowman's membrane.

In our own cases, the epithelium was also thinner than normal, infiltration of round cells (probably lymphocytes) was present, and the basal cells had lost their characteristic features and were flattened. As in Jaeger's case we, too, found little foci of debris of Bowman's membrane and migratory nuclei lying between the epithelium and Bowman's membrane (Case 3). Some sections showed a cavity in Bowman's membrane containing fluid and migratory cells.

Bowman's membrane, which remained in Elschnig's and in Jaeger's case, was also present in our own Cases 1, 2, and 3. The little foci of lymphocytic deposits within Bowman's membrane described by those authors have been found by us as well.

Parenchyma. Elschnig noted the parenchyma infiltrated with migratory cells and with necrotic processes of the same kind of cells, and the lamellae as well. He also found a repairing process consisting of division of the fixed corpuscles in the vicinity of the necrotic foci. The lymph spaces were dilated and contained an exudate of detritus, fine grains, and nuclear fragments. The lamellae were more or less normal.

Jaeger also noted an infiltrated parenchyma, especially near the epithelium and Descemet's membrane, but he observed only slight damage to the layers of the middle third of the cornea. The infiltrate consisted

mainly of lymphocytes and newly formed vessels. The lamellae of the parenchyma were only slightly altered, but the lymph spaces were edematous and contained nuclei of different kinds.

In our cases, the superficial layers of the cornea showed the most marked alterations and the middle layers exhibited less change, exactly as in Jaeger's case. As for the rest, we encountered the same changes as described by Elschnig and Jaeger at the parenchyma, namely cellular infiltration of lymphocytic type, interstitial edema, and dilated lymph spaces containing nuclei and cellular detritus.

In their older cases Stanculéano, Stock, and Watanabe made these observations:

The epithelium was almost normal, only swollen and with prongs penetrating the parenchyma. This picture coincides with that of our older Cases 4, 5, and 6.

Bowman's membrane followed the contour of the epithelium. Sometimes it was absent and sometimes thinner than normal. The defects of the membrane were replaced by groups of lymphocytes. We encountered exactly the same changes in our older cases.

In short, in recent cases of syphilitic interstitial keratitis, the number and shape of the epithelial cells is altered but Bowman's membrane remains. In older cases, the epithelium has regenerated but Bowman's membrane undergoes destructive processes.

The parenchyma in older cases undergoes several changes. Newly formed vessels which have their own walls appear; cellular infiltration is present; the lamellae are altered and replaced by wavy fibers. Sclerotic foci and newly formed tissue are encountered. The appearance of our own cases, studied by means of keratectomies, is consistent with those of the authors[2-6] who studied the cornea throughout in enucleated eyes.

SUMMARY

In five patients with luetic interstitial keratitis, 7 keratectomies were performed for biopsy material which was used to analyze the histologic changes taking place in several stages of the disease ranging from a clinical course of 25 days to 2 years.

Keratectomy is not an ideal means of investigation since it does not permit examination of the entire thickness of the cornea. However, since it can be performed without fear of damage to the patient, keratectomy provides a useful means for studying congenital syphilitic interstitial keratitis, a disease that has not been studied exhaustively yet.

The findings at the epithelium, Bowman's membrane, and parenchyma are analogous with those of other authors.

In the early stages, between 25 and 90 days, marked changes of the epithelium occur, characterised by infiltration of an exudate containing lymphocytes and erythrocytes which disarrange the orderly architecture of the epithelial cells. The epithelium is formed by 1 or 2 rows of cells in those places where the exudate had decreased or disappeared.

Bowman's membrane is not altered during this stage. It remains perfectly normal and stains evenly.

The parenchyma is also infiltrated by the same elements as the epithelium. The lymph spaces are enlarged and contain fine detritus. The lamellae appear to be not greatly altered, but edematous. Their fibers seem often to be swollen, giving thus a homogeneous appearance to the lamellae. In this stage, the nuclei of the normal cells of the parenchyma are swollen or show cariokinetic changes.

In more advanced stages, the epithelium seems to be repaired, since it either shows a normal or an increased number of layers. Epithelial prongs are seen within the parenchyma. Bowman's membrane undergoes marked changes; in places it has disappeared, or is disrupted, or has been reduced in thickness.

The parenchyma shows vascularization. The vessels have their own walls and some

of them present active blood currents; others have their lumen clogged following degenerative processes of their walls. A few lymphocytes and histiocytes are observed in the most advanced stage of the disease. The lamellar tissue is sometimes replaced by scar tissue.

Laprida 1159.

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PRESENT CONCEPT OF THE THERAPY OF OCULAR SYPHILIS*

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The dire need of a rapid and effective therapy of syphilis, brought on by the war years, stimulated intensive study and research along these lines, the results of which are far-reaching. A new interest in syphilis has been awakened and a new concept of its therapy is being established. In the midst of this evolution, it behooves us to survey the opinions of leading men in this field and to formulate conclusions which will guide us to a better understanding of its treatment.

TREATMENT OF SYPHILIS

PENICILLIN

In this treatment, penicillin plays a leading role. Its effectiveness as a treponemocidal agent has been definitely established. Its acceptance has been universal and enthusiastic and its evolution, since its inception,

has been rapid.[1] However, this antibiotic is still in its infancy and it would be unwise and even hazardous, at this time, to arrive at any definite and dogmatic decisions. During the past year, a pure form of the drug has become available to us as a calcium and sodium salt, and just recently it has been synthesized by Du Vigneaud and his fellow workers.[2] The various species of penicillin, namely: F, G, K, and X, are under carefully controlled investigation.[3, 4, 5]

At the present time most of our commercial fractions are of the G species. All fractions of penicillin are rapidly excreted in the urine and attempts are constantly being made to maintain its concentration in the blood over a longer period of time. The most effective and successful method has been the Romansky and Rittman formula.[6, 7] Hydrogenated oil is also used as a vehicle, but here the maintenance of high blood levels is less pronounced.

Caronamide, a drug which exerts an inhibitory effect on renal excretion by action on the tubules, is under observation.[8] At-

tempts by Kolmer and Rule[9] to develop a strain of Treponema resistant to penicillin have been unsuccessful. Experimentally, Eagle and others[10] found that fever therapy enhanced the action of penicillin, but this has not been borne out clinically.[11]

The effect of penicillin is lost in acid solutions, even as weak as a pH of 5 or 7. Thus combinations with adrenalin hydrochloride and boric acid should be avoided.[1] Herxheimer reactions occur very commonly with penicillin, but are mild in degree and generally manifest themselves as an increase in temperature, headache, and general malaise. Local manifestations may be more severe.

ARSENICALS

Likewise, observations made during the rapid 20-day and the 25-week treatment of syphilis, with arsenicals, have enlightened us on their use. It was noted that mapharsen was a safe and therapeutically effective arsenical, and that the toxic reactions, in spite of the rapidity of administration, were not marked. On the other hand, the use of pentavalent arsenicals (tryparsamide) has been abandoned because pharmacologic studies showed that it had to be reduced to the trivalent form to be effective; that it had no greater penetrability or affinity for the central nervous system than the trivalent form; and that it often caused permanent visual damage in spite of precautionary measures.[12]

BAL is reported by Eagle and Magnuson[13] to be quite effective in controlling the many toxic reactions which do occur in the heavy metal therapy, and it has been recently postulated by Friedham and Vogel[14] that the combination of arsenicals and BAL may give us a nontoxic drug for syphilis therapy.

THERAPY OF OCULAR SYPHILIS

To facilitate generalizations, we have divided the therapy of ocular syphilis into the treatment of the acute ocular conditions and that of the chronic ocular conditions. Thus,

before taking up the treatment of individual lesions in the eye we may say that the more acute the syphilitic lesion, the more effective penicillin or chemotherapy will be and, likewise, the more acute and severe the lesion, the more severe the Herxheimer reaction will be, if large doses of the antisyphilitic drug are used. This latter reaction is to be avoided in treatment, especially so in the eye, because it leads to intensification of the inflammation locally and to too rapid a tissue destruction with increased fibrosis, thus burdening recovery.

From these generally observed facts, our results will depend on how early we can institute treatment in the more acute lesions of syphilis, and upon avoidance of a therapeutic paradox by the use of too large an initial dose in the more severe acute lesions.

ACUTE OCULAR CONDITIONS

Interstitial Keratitis. Interstitial keratitis is included in the classification of acute conditions, although the question still remains as to whether it is due to the presence of the spirochete in the cornea or to allergic or toxic reaction. The lack of dramatic response to penicillin and the absence of any noticeable reaction when large initial doses of penicillin are used would lead us to believe that other factors, besides syphilis, play an important role. Comparative results of treatment can be noted in the recent statistical study made by Klauder[15] (Table 1). In this same survey it was shown that penicillin does not prevent an initial attack of interstitial keratitis, nor does it prevent involvement of the second eye or recurrences of the disease. In spite of the resistance of this condition to antisyphilitic therapy, it is generally agreed that intensive therapy is indicated, as soon as the diagnosis is made. This immediate and early treatment has continued to show better response and results according to most observers.

Since penicillin is as effective as any other drug and can be given in a shorter period of time without danger of toxic reactions,

it becomes the drug of choice. Local penicillin therapy by iontophoresis, subconjunctival injections, and penicillin packs have ardent exponents, but at the present time there is insufficient data to warrant any definite conclusions.

We know of impressive results obtained by the use of iontophoresis, and this was especially noted in the earlier cases in which treatment was started immediately. Fever therapy is widely accepted as favorably influencing the outcome of interstitial keratitis and can be used in any of its forms as an adjunct to penicillin. Of course, mydriasis must be maintained by atropine or scopolamine throughout the treatment. Tradition and lack of noticeable response to penicillin have turned some observers back to the use of the heavy metals.

Syphilitic Uveitis. Syphilitic involvement of the uveal tract occurs in the secondary or late secondary stage of syphilis. The difficulties encountered in proving the syphilitic etiology of uveitis have caused considerable variation in the interpretation of the results of therapy. Benedict[16] and others have shown that antisyphilitic therapy exerts a nonspecific action on uveitis, which may further complicate the evaluation of treatment. However, if more than a positive Wassermann reaction or a history of an old syphilitic infection were required for the basis of our diagnosis, our therapeutic results might be more uniform.

Klauder and Dublin[17] suggest that the most important criteria are: "(1) Demonstration of, or evidence pointing to, an early stage of syphilitic infection, (2) an inflammatory process of such character as to exclude, as far as is possible, other etiologic factors, (3) prompt effect of antisyphilitic treatment."

They observed a local intensification in the iritis in 70 percent of their cases following the administration of penicillin and neoarsphenamine. They purposely avoided large initial doses to prevent therapeutic paradox, and their observations were made by slitlamp examination.

The reaction followed within 8 to 24 hours after the drug was administered and consisted of an increased haziness in the cornea, an increase in the corneal precipitates, and an increase in the number of cells in the anterior chamber or an increase in the swelling of the iris.

Nodular iritis may be confirmatory evidence, but it does not occur frequently. It is more apt to be seen in cases in which the primary syphilis was insufficiently treated.

If the diagnosis of syphilitic uveitis is based on these considerations, the response to penicillin is dramatic; the inflammation disappearing in one or two weeks, without recurrence. It is important to initiate treatment with caution in the more severe cases, beginning with 5,000 to 10,000 units for the first 4 to 6 doses and then stepping up the dosage quite rapidly to the 50,000 unit dose. Less dramatic results are obtained with chemotherapy, but it is likewise very effective.

Fever therapy may be used in conjunction with penicillin, but Klauder[17] feels that it shows no definite advantage. In all cases, the treatment should be carried through its

TABLE 1

COMPARATIVE RESULTS OF TREATMENT OF INTERSTITIAL KERATITIS FROM
A STATISTICAL STUDY MADE BY KLAUDER[15]

Method of Treatment	No. of Eyes	Percentage of Final Visual Acuity		
		6/6 to 6/21	6/30 to 6/60	Less than 6/60
Untreated	185	55.1	37.0	12.0
Fever and Chemotherapy	95	84.2	8.4	7.4
Penicillin	97	84.5	11.3	4.2

entire course and not stopped when the uveitis had abated. Here again, mydriasis must be maintained.

Syphilitic Optic Neuritis. Syphilitic optic neuritis occurs more commonly in the late secondary stage of syphilis. It may occur with a syphilitic menigitis or be associated with a retinitis. It may also occur as a retrobulbar neuritis. If adequate antisyphilitic therapy is instituted early, the therapeutic results are good. We definitely feel that extreme caution should be taken to prevent too rapid a retrogression of the process with resulting increased fibrosis in the optic nerve. Herxheimer reactions should be avoided. Tryparsamide should not be used. Arsenicals have proved a satisfactory form of treatment, but more recently penicillin is being used with excellent results.

The initial dose of penicillin should be 10,000 units for the first 4 to 6 doses and then increased by 10,000 units with each successive dose until the 50,000- or 60,000-unit dose is reached. This dosage is maintained until a total of at least $2\frac{1}{2}$ million units has been given. Since appearance of optic neuritis may be the first sign of involvement of the nervous system, the patient should consult the syphilologist for the plan of his future treatment.

Many observers feel that fever therapy is definitely indicated at this stage of treatment and that it, with the penicillin, may check further progress of the neurosyphilis.

CHRONIC OCULAR SYPHILIS

Taboparesis with Ocular Involvement. Penicillin has been very effective in improving spinal-fluid abnormalities and certain of the clinical manifestations of neurosyphilis (more so than the results experienced by chemotherapy alone). Stokes[18] and Kateen and others[19] considered it equal to the effects of fever therapy. It offers many advantages over the induced fever techniques and has been substituted for it in many instances. However, it is generally felt that in the case of primary optic atrophy,

the combination of fever and penicillin should be employed.

The efficacy of penicillin therapy in the treatment of optic atrophy has not been established, and, until more evidence is obtainable, patients with this condition should receive immediate treatment with fever. The Kettering hypertherm has been advocated by some (Knight[20]). Epstein[21] has had excellent results with "blanket fever therapy," but malaria is generally believed to be the most effective (Moore,[22] Levin,[23] and Clark[24]).

It is logical to assume that, in the treatment of optic atrophy, the initial doses of the drug should be low and that treatment should begin as early as the diagnosis can be made. The therapeutic paradox may explain some of the cases of rapid loss of vision during the course of antisyphilitic therapy.

Perhaps, the greatest benefit that penicillin will offer in the therapy of primary optic atrophy will be the prevention of its occurrence by adequate and effective therapy in the primary stages of the disease, and the prevention of further involvement of the nervous system.

Syphilitic Optochiasmatic Arachnoiditis. There is a great deal of confusion in the literature concerning this condition. It is regarded by some to be the cause of primary syphilitic optic atrophy. The arachnoid adhesions are known to exist and have been demonstrated at autopsy and in exploratory operations. There is some question, however, as to whether or not the adhesions are responsible for the optic nerve atrophy. The clinical picture is not clearly defined and the symptomatology varies.

In all cases, there is a reduction of visual acuity. This loss of acuity may be rapid or insidious, unilateral or bilateral, and a central scotoma may or may not be present. The visual fields show variable changes, more commonly peripheral constrictions with a central scotoma.

Some observers present convincing evi-

dence of the occurrence of the arachnoid adhesions which tie down the optic nerves and compress the chiasm. One is more convinced when, after surgical freeing of the adhesions, the vision improves or the defect does not progress. It is difficult to understand why the adhesions do not reform in abundance after surgery and perhaps the improvement may be explained by mechanical stimulation of circulation in the optic nerve.

Bruetsch[25] has just recently published a very convincing paper in which he presents histologic and clinical evidence that primary syphilitic optic atrophy is essentially the result of inflammation in the optic nerve and chiasm, originating from a basilar syphilitic meningitis, which may or may not cause optochiasmal arachnoiditis, and that surgery is of little value. His suggested treatment is malarial therapy with a concomitant and subsequent course of penicillin, each course to consist of at least 5,000,000 units.

PITFALLS OF PENICILLIN THERAPY

Certain disadvantages in the use of penicillin must be realized.[26] Its widespread use in many minor conditions may mask an early syphilitic infection. This is particularly true in the routine treatment of gonorrhea. Sensitization reactions occur, according to Anderson,[27] in 2 to 5 percent of patients, varying from mild skin erythemas to the more serious exfoliating forms of dermatitis. Rare cases of laryngeal edema are recorded. In the more severe sensitization reactions, the drug must be discontinued, as it aggravates the patient and the disease.

Relapses have been reported to occur by Moore and others[28] in 3.2 percent of patients with seronegative primary syphilis, 5.0 percent in those with seropositive primary syphilis, and 9.8 percent in those with secondary syphilis. This fact necessitates a careful follow-up of the patient every 3 months for the first 2 years, and then yearly for 5 to 10 years. The "lulling of the patient into complacency"[26] by the rapid effect of penicillin therapy must be avoided.

SUMMARY AND CONCLUSIONS

Penicillin is an effective and convenient nontoxic antisyphilitic drug. In view of its recent synthesis and the probability of the development of therapeutically more active side chains, or of combining it with some of the heavy metals, its possibilities are far reaching. The results of its use in the early and acute lesions of syphilis involving the eye are very encouraging. Following the initial doses of penicillin, the intensification of the inflammatory process (constituting the Herxheimer reaction) in the eye is greater in the more acute and severe lesions, and should be avoided by small doses of the drug in the early stages of therapy.

Fever therapy still holds an important place in the therapy of ocular syphilis, being unsurpassed in the treatment of primary optic atrophy. Combined fever and penicillin therapy may prove to be the most effective method, especially in the late stages of syphilis.

It is important to keep in mind the necessity for careful follow-up treatment on all cases of syphilis regardless of the method of therapy and to remember that lapses, relapses and reinfections occur, which may be hazardous to the patient and to the public-health program.

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DISCUSSION

DR. NORMAN N. EPSTEIN (San Francisco): Dr. Harrington and Dr. Henry have presented an important and timely paper on the present concept of the therapy of ocular syphilis. While we, as individuals, may see only an occasional case of ocular syphilis, when such a case appears it is of utmost importance that we understand how to manage it promptly and effectively. Mismanagement or delay may be catastrophic as far as that patient is concerned.

The authors have stressed the place of

penicillin in the treatment of syphilis and there is no doubt that it is the greatest addition to the armamentarium of antisyphilitic drugs. It is now in its fifth year of use and, although a tremendous amount of research has been done upon its clinical application, the optimum time-dose relationship to this disease has not been determined. We know that it is a potent spirocheticide. The G fraction has this spirocheticidal property which is now available as crystalline penicillin G.

Penicillin G may be expected to be most effective in syphilitic processes where there are large numbers of Treponema pallida present and less effective in the degenerative and allergic effects of syphilis.

The rapid spirochete-killing property of penicillin G is emphasized clinically by the frequent development of the Herxheimer reaction as pointed out by the authors. Its importance in ocular syphilis is great. This reaction may be prevented or minimized by preparing the patient with a few weeks' treatment with bismuth therapy or by instituting penicillin therapy conservatively. It is our practice, when we wish to prevent the Herxheimer reaction, to institute penicillin therapy according to the following schedule: 1,000 units of aqueous penicillin G every 2 hours intramuscularly for the first 12 hours; 2,500 units every 2 hours for the second 12 hours; 5,000 units every 2 hours for the third 12 hours. If no untoward reaction occurs, the full dosage of 50,000 units every 2 hours for a total dose of 4.8 million units is given.

Ambulatory treatment with crystalline penicillin G in 4.5-percent beeswax and peanut oil may be used after the first 36 hours that aqueous penicillin has been given; 600,000 units as a single dose may be given for 10 to 20 days.

Frequently, it is advisable to combine artificial fever therapy with penicillin therapy in ocular syphilis, especially in interstitial keratitis and primary optic atrophy.

Inasmuch as we have had excellent results with artificial fever produced by mechanical means (the blanket method) I can see no reason for using malarial therapy. Engrafting one disease upon another in order to elevate body temperature is entirely unnecessary. The value of fever therapy in the treatment of ocular syphilis is well established clinically. Eagle has recently shown that elevation of temperature enhances the spirocheticidal effect of penicillin many times, both in vitro and in experimental animals. Clinical experience and experimental studies amply indicate that fever therapy has an important place in the treatment of ocular syphilis.

Penicillin should be most effective in acute arachnoiditis, optic neuritis, and acute iritis. In these conditions, spirochetes are present in abundance and penicillin should destroy them rapidly. In interstitial keratitis, where we are probably dealing with few organisms and an allergic reaction, and in primary syphilitic optic atrophy, where the process is degenerative, fever therapy will do the most good.

When it is possible to combine fever therapy with penicillin, we may expect our best results. The more rapidly this therapy is instituted the less residual damage we will have to deal with. This is especially true when progressive optic atrophy is present.

Something should be said about tryparsamide. This drug is contraindicated in ocular syphilis. Its position in the treatment of neurosyphilis has been almost entirely usurped by penicillin. We believe that tryparsamide has only a minor place in the syphilitic armamentarium.

Our neurosurgeons have treated a few cases of optic atrophy by release of arachnoidal adhesions. The results have not been striking. However, we have used this method of therapy only as a last resort and, therefore, the method has not been given a fair trial.

STREPTOMYCIN IN CLINICAL OPHTHALMOLOGY*

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This study on the use of streptomycin in the eye clinic at Fitzsimons General Hospital, Denver, was not limited to a specific type of eye disease. It was felt that a greater knowledge of streptomycin activity could be obtained by treating more than one condition.

Recent medical literature has reported the successful use of streptomycin in ocular affections. Being a relatively recent therapeutic agent, this antibiotic has been used, thus far, predominantly on experimental animals. It cannot yet be said that streptomycin has won a place for itself in the treatment of ocular diseases; only further work with this drug will justify its use in these cases.

It is significant that streptomycin is more bacteriostatic or bactericidal than penicillin for Gram-negative bacteria. Streptomycin is also effective against some of the Gram-positive organisms. Among the Gram-negative organisms that may be found in the conjunctival fornices are: Koch-Weeks bacillus, Bacillus influenzae, Morax's diplobacillus, Petit's diplobacillus, Neisseria gonorrhoeae, Neisseria catarrhalis, Neisseria intracellularis meningitis, pneumonia bacillus, pseudomonas pyocyaneus, and Brucella tularensis. Some of the Gram-positive organisms are: Pneumococcus, Staphylococcus, Streptococcus, Corynebacterium diphtheriae, Corynebacterium xerosia, Mycobacterium tuberculosis.

Leopold and Nichols[1] have shown that streptomycin will penetrate the ocular tissues quite readily when administered systemically and by iontophoresis. Abrading the cornea will permit penetration when the drug is

applied locally in drop form. Holt and Cogan[2] have shown that the corneal stroma offers little resistance to the passage of ions; whereas, the epithelium offers a relatively enormous resistance. Thus it is consistent that Leopold and Nichols should find increased penetration through the abraded cornea.

Alberstadt and Price[3] used streptomycin locally by instillation in a concentration of 10,000 µg. per ml. They found that the corneal ulcers treated with streptomycin healed in an average of 13 days, while those in the control group, treated without streptomycin, healed in 20 days.

Flippin[4] has also found that, when administered parenterally, streptomycin is detected in the intraocular fluids in concentrations approximating that level found in the circulating blood. This is important because penicillin penetrates poorly from the blood stream into the vitreous.[5]

Bellows and Farmer[6] report that streptomycin injections into the vitreous are well tolerated in concentrations of 500 µg. in 0.1 ml. saline. Local application of streptomycin in concentrations greater than 10,000 µg. per ml. delay the regeneration of the epithelium and promote scarring and corneal vascularization.

METHODS OF ADMINISTRATION

This report is a delineation of several methods of streptomycin administration in clinic and hospital patients. The methods are:

Local administration by iontophoresis of 50,000 to 100,000 µg. streptomycin per ml. of normal physiologic saline solution. A pad of cotton was placed over the eye and saturated

with the streptomycin solution. A 2 ma. galvanic current was used for 4 minutes, the positive electrode being applied to the eye pad. This was used in external and anterior-segment inflammations.

Parenteral administration by the intramuscular route. Parenteral administration of streptomycin, 1 to 2 gm. daily in 2 to 4 divided doses, given intramuscularly, was used in the more severe cases.

<div align="center">CASE REPORTS</div>

BLEPHAROCONJUNCTIVITIS

Case 1. Infection was controlled with two treatments of streptomycin iontophoresis. A 30-year-old white man developed contact dermatitis of the lid margins following the use of an underarm deodorant. A severe secondary blepharoconjunctival infection developed disclosing hemolytic Staphylococcus on culture. After the second iontophoretic treatment with 50,000 µg. streptomycin per ml. the condition was greatly improved and the culture was negative.

Case 2. A recurrent lid infection of two years' duration in a 45-year-old white man resisted all treatment including sulfathiazole and penicillin ointment. The culture was negative. Eleven treatments of iontophoresis with 100,000 µg. streptomycin per ml. showed temporary improvement during the time of treatment but relapsed immediately on cessation of therapy.

ACUTE CONJUNCTIVITIS

Ten cases of acute conjunctivitis were treated with streptomycin iontophoresis using 50,000 µg. per ml. on an eye pad. Cultures disclosed 2 cases each with Gram-positive nonhemolytic Staphylococci and hemolytic Staphylococcus aureus and 2 with nonhemolytic Streptococci; 1 case with hemolytic Staphylococci and diphtheroids, 1 with hemolytic Staphylococcus aureus and another with nonhemolytic Staphylococcus albus. Three cases were negative.

In 8 of the cases the symptoms and ob-

jective evidence of the conjunctivitis subsided in an average of 2 treatments apiece. In the 9th case a sensitivity reaction occurred with marked blepharoedema, but the infection was controlled. In the 10th case the condition progressed to an oculoglandular syndrome, wherein the cultures and smears were negative and streptomycin therapy was ineffective. The condition was thought to be of viral etiology. However, it resolved after 10 days of parenteral penicillin therapy.

Cultures were negative in 48 to 72 hours in 7 of the cases.

CORNEAL ULCER

Case 1. This ulcer developed in two days in a 23-year-old white man following an abrasion by a Christmas-tree branch. The culture revealed hemolytic Staphylococcus aureus. In spite of conservative therapy, which included hot-boric compresses, 1-percent atropine drops once daily, and sulfathiazole ointment, the ulcer increased in depth and diameter. After the third treatment with 100,000 µg. streptomycin by iontrophoresis, the pain disappeared and there was no further staining with fluorescein. The culture became negative in 48 hours. Healing was uneventful.

Case 2. A blow with the fist to the right eye of a 25-year-old white man produced an abrasion which progressed to form a corneal ulcer in 5 days. The culture revealed nonhemolytic Staphylococcus albus. The ulcer healed after the third streptomycin treatment with iontophoresis, using 50,000 µg. per ml. of streptomycin.

Case 3. A third breakdown at the site of an old ulcer in a 22-year-old white man was completely healed with 6 treatments of streptomycin iontophoresis, using 50,000 µg. per ml. The culture was negative before therapy was begun. However, a 4th breakdown occurred three weeks later. This, likewise, was controlled by streptomycin iontophoresis, this time in 7 treatments, with no further recurrences in 3 months. The etiology of this ulcer was not known. Although a herpetic

type was considered, the corneal sensitivity was not altered.

KERATITIS

Case 1. A case of sclerotic keratitis over the lateral limbal margins of both eyes was seen in a 33-year-old Negro (fig. 1). Although the keratitis was of 5 years' duration, he complained of a dull ache, pruritus, and redness in both eyes for two months. The first strength Mantoux reaction was 2 plus. The culture was negative. At the time of the first consultation, the patient was using sulfathiazole ointment. He was given 2 gm. streptomycin parenterally daily for one month. In one week the eye ache, pruritus, and redness disappeared. At the end of a month, the conjunctival vessels were less congested and the limbal granulation tissue was greatly reduced (fig. 2). Streptomycin was then discontinued.

Within a week after cessation of treatment, a relapse occurred. Streptomycin therapy was resumed for another month with resulting complete quiescence of the lesions with minimal granulation tissue remaining at the limbus. The Mantoux reaction continued to be 2 plus. Visual acuity before and after therapy was 20/20 in each eye. Five months' observation showed no recurrence of the lesions or symptoms.

Case 2. A case of interstitial keratitis of one month's duration was seen in a 22-year-old American Indian. It was thought to be tuberculous. The culture was negative. The patient had been given penicillin ophthalmic ointment at a station hospital. He complained of a constant dull ache, photophobia, and epiphora in both eyes. Visual acuity was: O.D., 20/60; O.S., 20/25, uncorrectible. The cornea showed cloudy opacification and deep neovascularization of the propria, bilaterally. The first strength Mantoux reaction was 3 plus; Kahn test was negative. Streptomycin iontophoresis was begun, using 100,000 µg. per ml. Within one week photophobia, epiphora, and eye ache were greatly diminished. After one month of therapy, the lesions were

smaller and less dense. The blood vessels had begun to obliterate. The lesion in the left cornea cleared very well, while the right cornea was somewhat scarred in its deeper layers. Visual acuity was: O.D., 20/80; O.S., 20/20, corrected. The first strength Mantoux reaction was still 3 plus. A total of 42 treatments had been given.

Case 3. This 54-year-old white woman complained of moderate pain and loss of

Fig. 1 (Schultz and Grunwell). A case of sclerosing keratitis before streptomycin therapy.
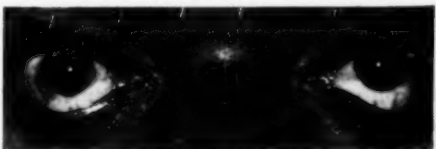
Fig. 2 (Schultz and Grumwell). The same case as in Figure 1 following streptomycin therapy.

vision in her left eye of two weeks' duration. Examination disclosed disciform keratitis with corneal anesthesia. The culture was negative and the first strength Mantoux reaction was 4 plus. Therapy included 1-percent atropine drops used once daily and iontophoresis with 50,000 µg. streptomycin per ml. in normal saline once daily. At the end of 6 treatments, the pain had disappeared and the lesion had become smaller. In fact the patient felt that her eye was so much improved that she decided to return to her Christian Science practitioner for further healing.

IRITIS

Case 1. Pain and slight visual loss in the left eye for 3 days was the complaint of a

35-year-old white man, who had recently recovered from pulmonary tuberculosis. Examination showed many mutton-fat keratic precipitates with many cells in the anterior chamber; the iris was edematous and sluggish in action. Because the patient had been up and around a short time, hyperpyrexia was considered unsafe.

Conservative therapy including 1-percent atropine drops once daily and hot-boric compresses was of no avail. One gm. streptomycin hydrochloride was given intramuscularly. That night the patient developed severe chills, fever, hemorrhagic bullae on his hands, and was practically prostrate. The patient had two such attacks. One hundred mg. of pyribenzamine and 10 cc. of calcium gluconate were given 3 times daily. Eight days later, all evidence of the previous iritis, including the keratic precipitates had disappeared.

The remarkably favorable results should be attributed to the patient's streptomycin allergy which caused the severe fever reaction. He had not been given streptomycin for tuberculosis. His general condition was unaffected. The iritis did not return during one month's observation.

UVEITIS

Case 1. This 55-year-old white man was operated for removal of a completely luxated Morgagnian cataractous lens. Upon attempted removal, the tense capsule ruptured just as the lens passed through the lips of the corneoscleral section. One week after surgery, corneal edema was quite marked. There were many cells in the anterior chamber and there was an increase in keratic precipitates from day to day. A retropupillary membrane which was present became quite dense at the end of two weeks. The patient complained of pain and tenderness of the eye. The culture and smear were negative.

Treatment consisted of 1-percent atropine drops, once daily. At the beginning of the third week, daily streptomycin iontophoresis, using 100,000 μg. per ml. was begun. After

10 treatments, the corneal edema and aqueous flare was less marked. The retropupillary membrane became thinner and, in 16 treatments, this membrane had completely disappeared. The subsequent course was uneventful.

Case 2. This 27-year-old white man complained of pain, tenderness, and photophobia in the left eye of 5 days' duration. He had had two such attacks previously, the first 20 years ago, the last one 4 years ago. Examination showed visual acuity in the left eye to be 20/50, uncorrectible, and signs of acute iridocyclitis with evidence of previous inflammation in the form of posterior synechias. The first strength Mantoux reaction was negative. Iontophoresis with 100,000 μg. streptomycin per ml. was begun 2 times daily. One-percent atropine drops once daily and hot-boric compresses three times daily were also begun. After five treatments of streptomycin iontophoresis, pain and tenderness were greatly relieved, corneal edema was reduced, keratic precipitates were fewer, and the aqueous flare was less marked. After 21 treatments, examination showed that the acute inflammation had subsided. Visual acuity was 20/30 in the left eye, uncorrectible.

Case 3. This 21-year-old white man, a patient with a minimal pulmonary tuberculosis, complained of hazy vision in each eye of one month's duration. Examination showed a visual acuity of 20/40 in each eye, correctible to 20/20. The slitlamp examination of the right eye disclosed a moderate number of keratic precipitates and many cells in the anterior chamber and vitreous. The left eye showed a small number of cells in the vitreous. The fundi were normal.

The presence of pulmonary tuberculosis contraindicated the use of hyperpyrexia. Therapy consisted of 1-percent atropine drops once daily, hot-boric compresses 3 times daily, and 1 gm. of streptomycin in 2 divided doses given parenterally. After one month of therapy, the patient no longer complained of hazy vision. Visual acuity was

20/30 plus in each eye, correctible to 20/15. Slitlamp examination of the right eye showed only a few remaining cells in the anterior chamber and the vitreous. No cells were found in the left eye.

Case 4. This 32-year-old white man complained of redness and blurring of vision in the right eye for a period of 3 weeks. Visual acuity of the right eye was 20/25, uncorrectible. The first strength Mantoux reaction was negative. Examination disclosed the presence of an anterior uveitis and a secondary glaucoma. Therapy consisted of cycloplegia and hyperpyrexia. It was finally necessary to resort to surgical intervention and an Elliot trephining operation was performed to control the tension. One month after surgery there was recurrence of the anterior uveitis with rise in tension. Thirteen treatments of streptomycin iontophoresis, using 100,000 μg. per ml. showed no regression of the uveitis. The condition was finally brought under control with the use of epinephrine bitartrate and adequate massage.

Case 5. This 42-year-old white man complained of loss of vision of the left eye 13 years ago following trauma. He had had a dull ache in this eye for several weeks. Visual acuity in the left eye was light projection. Examination disclosed the presence of many old and new keratic precipitates and a small number of cells in the anterior chamber; however, there were no synechias present. The iris was atrophic and a mature cataracta complicata was apparent. Intraocular pressure was 29 mm. Hg (Schiøtz). The first strength Mantoux reaction was 1 plus. Treatment consisted of 1-percent atropine drops and iontophoresis with 50,000 μg. streptomycin per ml. once daily. After the third treatment, the dull eye ache subsided and the tension dropped to 16 mm. Hg (Schiøtz). No positive findings were noted with the slitlamp although, after 28 treatments, there were fewer keratic precipitates and these were old. No cells were seen in the anterior chamber. The patient stated that his eye was subjectively much improved.

CHOROIDITIS

Case 1. Circumpapillary choroiditis in a patient with minimal pulmonary tuberculosis responded very well to parenteral streptomycin. This 21-year-old Negro complained of blurring vision in each eye of one week's duration.

Visual acuity was 20/20 in each eye. Slitlamp examination showed the anterior segment to be normal, but there were many cells in the vitreous of both eyes. Ophthalmoscopic examination disclosed hyperemia of both papillae with peripapillary edema worse in the left eye. There was exudate around the left disc. Moderate venous engorgement was present. Bilateral perimacular edema was also present. Visual field changes were consistent with findings of circumpapillary choroiditis. Hyperpyrexia was contraindicated because of the presence of pulmonary tuberculosis.

Treatment consisted of 1-percent atropine drops once daily, hot-boric compresses 3 times a day, and 50,000 units of penicillin intramuscularly every three hours. The condition was definitely worse after one week.

At the beginning of the second week, 2 gm. streptomycin were given daily in 4 divided doses. Within two weeks, improvement was noted, and there was regression of the peripapillary and perimacular edema. Peripheral and central fields showed marked recovery. The vitreous opacities cleared considerably. Streptomycin was continued for a longer period than the ocular disease indicated because of a subsequent improvement in the pulmonary tuberculosis. The choroiditis showed complete recovery in one month, but streptomycin was continued for 42 days. Visual acuity was 20/20 in each eye, uncorrected. No recurrence of the ocular condition was noted in 5 months.

EALES'S DISEASE

Case 1. A case of recurrent retinal periphlebitis was treated with parenteral streptomycin without improvement. This 22-year-old Negro, a patient with questionable pul-

TABLE 1

Results obtained with streptomycin therapy in various ocular diseases

Condition Present	Case Number	Age	Duration of Complaint	50,000 µg./ml.	100,000 µg./ml. (Iontophoresis)	No. Rx for Improve	No. Rx for Recovery	Not Improved	Parent. Strep. Dosage	Recovery Time	Complications	Culture	Hem. Staph. Aureus	Nonhem. Staph. Albus	Hem. Staph. & Dipith.	Nonhem. Strep.	Nonhem. Strep. & Hem. Staph.	Mantoux	Recurrence	Observ. follow. R.
Blepharoconjunctivitis	1	30	1 wk.	X	X	2	5	X			None	—	X							1 mo.
	2	45	2 yrs.								Cont. Derm.									2 mo.
Acute conjunctivitis	1	19	2 da.	X		2	4				None	—								2 mo.
	2	32	4 da.	X		1	2				None		X							3 wk.
	3	8	2 da.	X		1	3				None			X						1 mo.
	4	30	1 da.	X		1	1	X			None		X							1 mo.
	5	30	1 wk.	X		2	4				None				X	X	X			1 mo.
	6	43	1 mo.	X		2	4				None									2 mo.
	7	19	1 wk.	X		2	4				None									1 mo.
	8	25	1 da.	X		3	5				None									1 mo.
	9	25	2 da.	X							Cont. Derm.									1 mo.
	10	25	1 da.	X		1	Dis-con.													1 mo.
Corneal ulcer	1	23	2 da.	X	X	3	4				None	—		X						2½ mo.
	2	25	5 da.	X		3	3				None		X							1½ mo.
	3	22	1 da.			6	6				None									2 mo.
Keratitis	1	33	5 yrs.			12	42		2 gm. daily	2 mo.	None	—						2+	X	5 mo.
	2	22	1 mo.	X	X	6		X			None	—						3++	(X)	1 mo.
	3	54	2 wk.								None							4+		1 wk.
Iritis	1	35	3 da.				Dis-con.	Incomplete	1 gm. daily		Severe system. react.	not done								1 mo.
Uveitis	1	55	3 wk.		X	10	16		1 gm. daily	1 mo.	Pain Edema	*						— TB Pulmon.		2 mo.
	2	27	5 da.		X	5	21				None	*						— TB		1 mo.
	3	21	1 mo.								None	*								4 mo.
	4	32	3 wk.		X	3	28?	X			None	*						1+		3 mo.
	5	42	3 wk.	X							Sl. Corn. stain.									2 mo.
Choroiditis	1	21	1 wk.					X	2 gm. daily	2 wk.	None	*						Pulmon. TB		4 mo.
Eales's disease	1	22	2 wk.						2 gm. daily		Facial derm.	*						3+		5 mo.
Intravitreal foreign body	1	21	8 hr.						1 gm. daily	2 wk.	None			X						1 mo.

monary tuberculosis, complained of poor vision in the left eye of 2 weeks' duration. Visual acuity was 20/20 in the right eye and 6/400 in the left eye, uncorrectible. Ophthalmologic examination showed the right fundus to be normal while the left showed peripheral venous perivasculitis. The first strength Mantoux reaction had been 3 plus when the patient was admitted to the hospital 6 months previously.

The patient was given 2 gm. streptomycin parenterally daily for 26 days. Following this period, the right eye began to show venous perivasculitis and hemorrhages increased in the left eye. Vision in the right eye was 20/20; hand movements in the left eye. The condition became progressively worse in spite of streptomycin and strict bed rest. Rutin was begun, but this too proved ineffectual. At the last examination, 6 months after the onset of symptoms, massive vitreous hemorrhages in each eye had reduced visual acuity to light projection in the right eye and the ability to count fingers at one meter with the left eye.

INTRAOCULAR FOREIGN BODY

Case 1. This 21-year-old white man was hammering a chisel when a fragment from the hammer flew into his left eye. Examination disclosed a jagged perforation of the sclera through the internal rectus muscle. The vitreous was presenting. Ophthalmologic examination disclosed air bubbles in the vitreous and massive vitreous hemorrhage. No foreign body was seen. Following X-ray localization, removal of the intraocular foreign body through the perforation was successfully performed. Cultures revealed a nonhemolytic Staphylococcus albus.

Further therapy consisted solely of strict bed rest and 1 gm. daily of streptomycin hydrochloride given parenterally. The medication was continued for two weeks. There was no evidence of intraocular infection and the eye had begun to whiten. Three days after stopping streptomycin, a massive vitreous hemorrhage occurred, obscuring the pre-viously visible fundus. At the last examination, 6 weeks after the injury, the sclera of the injured eye was almost as white as the normal eye and the vitreous hemorrhage was absorbing slowly; there was no evidence of inflammation nor of phthisis.

COMMENT

The advent of a new drug in the field of ocular therapeutics is often similar to a chain reaction. First there is skepticism, then acceptance, followed by over-enthusiasm, ending in indifference.

Those who work with a new drug often fail to realize that many ocular diseases are self-limiting. It follows, then, that cures attributed to the drug at hand should be viewed with caution because the error of clinical observation is high. The enthusiasm of the experimenter should be tempered by the criticism of the skeptic.

The clinical use of streptomycin herein presented is significant in that the course of ocular disease was favorably altered in the majority of cases studied.

The rational in using streptomycin in concentrations of 50,000 and 100,000 µg. per ml. of normal saline solution, 5 and 10 times greater than that recommended by Bellows and Farmer,[6] lies in the fact that a pad saturated with streptomycin is placed over the partially closed lids. Thus, the tears diluted the streptomycin as it came in contact with the cornea and conjunctiva. It was felt that not only was local application achieved but that the tarsal glands, so often the nidus for infection, were in some measure penetrated by the antibiotic.

The first case of acute secondary blepharoconjunctivitis culturing hemolytic Staphylococcus responded very well to streptomycin. The second case of chronic blepharoconjunctivitis was only temporarily improved while on treatment. This latter patient developed a contact dermatitis of the lids after the 11th treatment; this is not uncommon, as indicated by Strauss and Warring.[7]

The 10 cases of acute conjunctivitis were treated with iontophoresis using 50,000 μg. of streptomycin per ml. of normal saline. All but 3 cases showed positive cultures. Marked improvement was noted after an average of 2 treatments in 8 of the cases. The 9th case developed contact dermatitis of the lids, but the culture was negative after the first treatment. The 10th case was thought to be viral in etiology; no response was obtained. The ideal condition would have been to run a series of control studies without any treatment and another series using penicillin, but this was not possible. All we can surmise is that, on the basis of clinical observation and bacteriologic studies, improvement was not only achieved but accelerated.

The satisfactory results obtained in the healing of corneal ulcers indicated that our streptomycin concentrations did not discourage epithelization, and were apparently effective against Gram-positive organisms. We agree with the findings of Alberstadt and Price[3] in that the "duration of pain was shortened, healing of the ulcer was accelerated, and total hospitalization was shortened."

Parenteral streptomycin was effective in controlling a case of sclerosing keratitis—the etiology very likely was tuberculous. The tuberculin skin test was positive and unchanged before and after therapy. Is it possible that the allergenic focus was altered by the streptomycin and thus changed the type of tuberculoprotein produced? Or was the lesion on the eye tuberculous per se? Further investigation is certainly indicated along these lines.

It is pertinent at this point to recognize the activity of streptomycin against the tubercle bacillus. It had been demonstrated by Fisher[8] and other investigators[9] that tubercle bacilli isolated from a total of 130 patients prior to therapy were uniformly inhibited by 1 μg. or less streptomycin per ml. The literature[1, 4] and our own studies give ample evidence of the high intraocular concentration of streptomycin. Therefore, is it not conceivable that streptomycin may favorably affect the course of the ocular tubercle or of ocular disease due to tuberculin sensitivity? Several of our case studies indicate that this may be so. Streptomycin iontophoresis appeared to improve the course of a tuberculous interstitial keratitis and a disciform keratitis. First strength Mantoux tests in these cases were 3 and 4 plus, respectively.

A patient with healed pulmonary tuberculosis was found to have iritis with mutton-fat keratic precipitates. A single dose of one gram of parenteral streptomycin produced a very severe and dangerous anaphylactoid reaction, characterized by high fever (105°F.), morbilliform rash, blotchy erythema, and generalized malaise. To avoid a reaction such as this, it would be advisable to skin test each patient prior to therapy.

Five cases of uveitis were seen. Four were treated with streptomycin iontophoresis and one, a patient with pulmonary tuberculosis, was treated with parenteral streptomycin. Four of the cases improved under therapy.

One case of circumpapillary choroiditis in a patient with pulmonary tuberculosis responded favorably to parenteral streptomycin wherein previous conservative therapy had failed.

A patient with Eales's disease did not respond to parenteral streptomycin after 26 days of treatment. The disease progressed to cause almost complete blindness.

A patient was seen with an intravitreal metallic foreign body, with vitreous presenting at the point of entrance through the sclera. The culture was positive for non-hemolytic Staphylococcus albus. Parenteral streptomycin was given for two weeks after removal of the foreign body. No vitreal infection or phthisis had occurred after one month's observation.

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FUNDUS LESIONS IN TUBERCULOUS MENINGITIS AND MILIARY PULMONARY TUBERCULOSIS TREATED WITH STREPTOMYCIN

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As early as 1942, I had called attention to the frequency with which chorioretinal tubercles are found in miliary pulmonary tuberculosis and in tuberculous meningitis.[1] These lesions had been fully described in 1867 by Bouchut[2] but they had been apparently forgotten by some, and their existence denied by others.

As treatment with streptomycin was started on such cases in the hospitals of Paris, I suggested the importance of ophthalmoscopic examination from the diagnostic, prognostic, and even therapeutic standpoints. It was indeed possible to think that the evolution of the chorioretinal tubercles, following treatment with streptomycin, could be similar to that of the meningeal or pulmonary lesions.

At the same time as Debré, Monbrun, and Lavat[3] were studying (in the Hôpital des Enfants Malades) the fundi of 135 such cases, I carried on a similar study in the specialized departments of the Hôpital de la Pitié and the Hôpital de la Salpétrière, in the services of M. Decourt and M. Fouquet. At the Pan-American Congress of Ophthalmology at Havana, I reported the first results; but, since then, I have examined a great number of cases with lesions either in the chorioretina or in the optic nerve.

CHORIORETINAL LESIONS

The chorioretinal lesions are of three main types, all of which represent miliary tuberculosis, as described long ago by Bouchut. If these lesions have not been seen by some observers, it is due to the fact that the examination of young, severely ill, semicomatose, and photophobic patients is quite difficult. A complete mydriasis, repeated examinations in the course of the disease, and a great deal of patience are essential.

The first type of lesion seen is the small miliary tubercle. It is round, situated near the bifurcation of vessels, white or yellowish, with indistinct edges, and with a diameter rarely exceeding one-half disc diameter. It may be found anywhere in the retina but most often is located near the posterior pole, in contact with or close to the disc. This tubercle is slightly elevated above the level of the retina; it may be single, but is more often multiple, and distributed in both eyes. The optic nerve is somewhat hyperemic, with blurred margins. Functional signs are almost absent. Since there are usually no

subjective symptoms, even in conscious patients with miliary pulmonary tuberculosis, only a systematic search for the lesions will disclose them.

In the second type, more often noted than the tubercles, the retinal lesion is formed by one or more small white spots with blurred edges, not elevated above the retina, of more irregular shape than the tubercles. They may be round but are generally more or less triangular. In certain cases, especially in miliary tuberculosis with meningitis, the whole posterior pole of the eye is spotted with such lesions which may number as many as 10 or 20. More commonly, however, only 5 or 6 are noted and present equally in both eyes.

The third type of lesion is found more rarely. It is a single, isolated tubercle, measuring 1 to 2 disc diameters in size. It is rounded and somewhat elevated above the retina. This tubercle is yellowish-white in color, and its edges are fairly well defined.

One should mention, in addition (as has been observed by Monbrun and Lavat), the occasional presence in these patients of small chorioretinal patches of the atrophic type, with some pigmented edges, which may be considered as healed tubercles.

Optic-nerve lesions

Lesions of the optic nerve are less frequent than those in the retina. However, as I have already stated, the presence of a chorioretinal tubercle is often associated with a certain degree of papillary edema characterized by congestion of the nervehead and blurred edges. More rarely, the appearance may be that of a choked disc, especially in the cases of tuberculous meningitis where streptomycin treatment has led to partitioning by meningeal adhesions. In these cases with meningitis, the choked discs often resemble those with intracranial tumor. Finally, in a few isolated cases, I have noted the presence of an optic atrophy, with well-defined margins. I am not sure what the pathogenesis of these cases may be.

Evolution of the chorioretinal lesions

Before streptomycin therapy was introduced, death occurred quite rapidly and, therefore, healing of the tubercle of the choroid was seen only exceptionally. Since the use of streptomycin, however, it has been possible to follow these lesions for weeks or months.

Contrary to what was expected, streptomycin seems to have a very irregular action on the evolution of the chorioretinal tubercles. In some cases, I have seen the tubercles become paler, then disappear completely without leaving a trace; in others, the evolution started with a pigmentation at the center of the lesion as a black spot, then extended toward the periphery, finally leaving a small atrophic area edged with pigment or centered by a black spot. This evolution of the tubercle toward healing was noted in only a small number of cases, and paralleled improvement of the general health.

In 5 of 16 cases, the tubercles disappeared or became healed with pigmentation as the condition of the patient improved after several weeks of treatment. In 9 cases, the lesions were not modified by the use of streptomycin, and the tubercles remained without apparent change 3 or 4 months after the start of the treatment, even though 2 gm. of streptomycin were used daily. Finally, in 2 cases there was dissociation between the evolution of the chorioretinal tubercles, which disappeared, and the general condition which declined and ended in death.

Tubercles of the choroid were even seen to appear in the course of the treatment. In a case which had been checked and treated for several weeks, with improvement in the general condition, several tubercles observed at the first examination healed or disappeared, then suddenly multiple tubercles developed in both eyes as the treatment was continued regularly.

In some patients, dismissed from the hospital after apparent cure of their meningitis or miliary pulmonary tuberculosis and in whom tubercles disappeared or even in whom

none were seen during the course of the treatment, who were reëxamined several weeks after discontinued treatment, chorioretinal tubercles were noted later. This proves that the tuberculous process was not entirely extinguished and that a recurrence was imminent.

FREQUENCY OF THE CHORIORETINAL LESIONS

In my preceding article,[1] I reported that chorioretinal tubercles had been noted in 72 percent of the cases of miliary tuberculosis without meningeal symptoms, and 40 percent of the cases of tuberculous meningitis. These examinations, however, were made on severely ill patients, often in the last days of life, when an efflorescence of miliary lesions occurs. In addition, the statistics were derived from a limited number of patients.

The centralization of the cases in specialized departments, for treatment with streptomycin, has enabled me to observe a larger number of patients, adults as well as children.

My study was made on 226 patients (103 adults and 123 children). I noted tubercles in 79 cases (35.0 percent; 29 percent in adults, 39.9 percent in children). I have further divided my cases, as follows:

1. Pure miliary tuberculosis without meningeal signs—37 cases of this type were examined; 18 had tubercles (48.7 percent; 33 percent of adults, and 65.7 percent of children).

2. Military tuberculosis with meningitis—29 cases were observed, of which 20 presented chorioretinal tubercles (68.9 percent; 75 percent of adults, and 61.5 percent of children).

3. Tuberculous meningitis without pulmonary signs—160 cases were examined; 31 presented chorioretinal tubercles (19.3 percent; 17.4 percent of adults, and 20.8 percent of children).

The appearance of tubercles is a little more frequent in children, as compared with the adults. If the frequency of the tubercles found in meningitis is smaller than that of published accounts, it is due to the fact that the cases of meningitis are now directed earlier to a specialized department for streptomycin treatment at a stage when tubercles of the choroid are rare and, under the influence of the treatment, do not develop.

There is no appreciable difference in frequency between the sexes.

FREQUENCY OF OPTIC-NERVE LESIONS

The fairly frequent observation of a slight blurring of the disc margins, when tubercles of the choroid are present, has already been mentioned. However, not infrequently, in addition to the slight edema, a real papillitis or choked disc has been observed. In 5 cases of tuberculous meningitis, I noted the development of optic atrophy during the course of treatment.

It is obvious that, in miliary pulmonary tuberculosis, involvement of the optic nerve is exceptional. Only one case was noted (2.7 percent) and it is probable that the patient might have developed meningeal signs, if follow-up had been complete.

In miliary pulmonary tuberculosis with meningeal involvement, the optic nerve was affected in 10.3 percent of cases.

In tuberculous meningitis, this complication is much more frequent. In 160 cases, 45 had such lesions, or 28.1 percent; and in 5 cases (3.1 percent), an optic atrophy was present. These cases of optic atrophy may give rise to a discussion as to the etiology. In my communication to the Pan-American Congress at Havana, I introduced the hypothesis that the lesion may be due to the toxicity of streptomycin, similar to neuritis of the eighth cranial nerve which is known to develop. Four such cases were in children aged 3, 3½, 5, and 6 years. I examined these children upon their admission; their fundi were considered normal. Three of these cases had tuberculous meningitis, and the fourth miliary pulmonary tuberculosis with meningitis. The dosages of streptomycin were 1.5

to 2 gm. daily, by intramuscular injections, and 0.2 gm. intrathecally. In all 4 cases, after 2 weeks of treatment, a pallor of the disc was noted without preceding papillitis. Slowly the discs became atrophic, with loss of sight. In 1 of the cases, treatment with streptomycin was stopped, with a resulting slight improvement in the visual acuity; but in the 3 others blindness with optic atrophy became permanent. Since formulation of the hypothesis of toxic optic neuritis, anatomic evidences were obtained in 2 cases. The optic nerves were sheathed by a false membrane, thus forming a real optico-chiasmatic arachnoiditis. The possibility of toxic neuritis due to streptomycin cannot be dismissed entirely; but the fact that this complication is not seen in the large group treated and having no meningeal signs leads one to believe that the etiology of these cases of neuritis may be the meningitis. The presence of this complication in these patients is due to the extension of life afforded by the treatment of meningitis by streptomycin.

CONCLUSION

The systematic examination of the fundus oculi, in tuberculous patients treated with streptomycin, can bring out significant observations on the course of the disease.

The appearance or the discovery of chorirorentinal tubercles has considerable prognostic importance, as it forecasts a meningeal complication in miliary pulmonary tuberculosis and is an index of severity of the form of the disease in tuberculous meningitis.

It is necessary, after discontinuation of the treatment with streptomycin, in patients considered as cured, to have periodic ophthalmoscopic examinations. The appearance of a chorioretinal tubercle preceding a recurrence of the systemic disease, by days or weeks, leads thereby to the earlier resumption of treatment.

In a fairly large number of cases, evolution of the chorioretinal tubercles paralleled the evolution of the pulmonary or meningeal tuberculosis; but the relation is not constant and, from the state of the fundus lesions, one cannot deduce the state of the systemic lesions.

The lesions of the optic nerve, especially choked disc which is fairly frequent, lead one to believe that, in these cases of meningeal blocks by adhesions or in cases of block of the third ventricle, an operation may become necessary to place in situ the drug which cannot pass through the meningeal partitions.

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REMOVAL OF INTRAOCULAR NONMAGNETIC FOREIGN BODIES*

WITH A REPORT OF SIX CASES

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Any type of intraocular foreign body may test the skill and patience of most ophthalmologists. This is doubly true when the foreign body is nonmagnetic. In many cases the surgeon is perplexed and at a loss as to what procedure to follow, particularly when the patient still has useful vision present in the injured eye.

This problem was particularly important during the recent world war when the incidence of nonmagnetic intraocular foreign bodies was very high. This was pointed out in Wilder's[1] report concerning 150 enucleated eyes which had been sent to the Institute of Pathology, U. S. Army Museum. The increased use of alloys in industry and in civilian life also increases the incidence of inocular nonmagnetic foreign bodies and makes this problem more important to the ophthalmologist.

Jackson[2] has said "the earliest possible removal of the foreign body is the first thing to be considered in nearly all cases and it usually should be done at any cost, even to the removal of the eye." de Schweinitz[3] stated that "while foreign bodies in the background of the eye may be tolerated for long periods of time with retention of good vision they never can be trusted, as they are liable to cause degenerative changes." Knapp[4] felt very much the same as these two authors. This feeling has become more or less universal among ophthalmologists, particularly when the foreign body is copper which is believed to cause irritative and later degenerative changes, including chalcosis, when left in an eye. This was first pointed out by Leber[5] over 50 years ago. Purtscher,[6] in 1918, called attention to chalcosis lentis or copper cataract. Schultz[7]

more recently has described this condition as bilateral. Sympathetic ophthalmia has been considered a very likely complication in these cases; however, I am not so sure that this danger is as great as we formerly thought it to be.

Bulson[8] doubted the necessity for removal of all foreign bodies. He felt that every case should be considered separately. Of course, there are many types of inert nonmagnetic foreign bodies such as glass, stone, zinc, wood, and so forth, the removal of which from the eye is not always essential, but depends upon the localization and size of the foreign body.

I have had under my observation for over 16 years a man who has had a small piece of zinc embedded in one eye. This is in the retina near the optic disc, with no evidence of any ocular irritation or degeneration. Nevertheless, I think we can all agree that, if a foreign body is present in an eye and if it can be removed without too much destruction to the eye, its removal should be attempted. I feel that this is especially true when the foreign body appears to be copper.

I have had two cases under my observation for the past 3 or 4 years, one of which has a small piece of copper (dynamite cap) in the lower anterior vitreous as localized by the Sweet localizer. This cannot, however, be seen with the ophthalmoscope. This case showed a definite chalcosis lentis with an irregular starlike yellow pigmentation on the anterior capsule of the lens when it first came under my observation. After several consultations, it was decided to make no attempt to remove the foreign body, since it was not visible with the ophthalmoscope and also since the vitreous in the lower portion was so very cloudy. However, if

and when the vitreous clears enough to afford a view of the foreign body, we will attempt its removal, using the first method about to be described.

The second case has a piece of copper (a fragment of a 22-caliber cartridge shell) which is localized in the sclera far posteriorly. Again, the foreign body cannot be seen with the ophthalmoscope. Dr. Zentmayer has seen this case in consultation and advised conservative treatment and observation which has been followed to date. The eye remains quiet.

METHODS OF REMOVAL.

Numerous methods for the removal of nonmagnetic foreign bodies from the eye have been attempted in the past. The five principal ones which have been reported are: (1) Direct observation with the ophthalmoscope while using forceps through a posterior sclerotomy; (2) use of the biplane fluoroscope; (3) removal with the ophthalmic endoscope; (4) removal by use of transillumination; (5) removal of small foreign bodies from soft lenses by means of a large needle and suction.

FORCEPS THROUGH A POSTERIOR SCLEROTOMY

The first of these methods is unquestionably the oldest and has probably been used by more ophthalmologists than any of the others. Greenwood[9] stated that he used this method to extract copper from the eye in two cases more than 20 years ago. He also stated that the forceps he used had cup-shaped ends.

Technique. The Parker electric hand magnet is applied to the globe while observing the foreign body with the ophthalmoscope. The current is turned on and off and the foreign body is carefully observed to detect any response. In the absence of any response, it is concluded the foreign body is nonmagnetic.

A retrobulbar injection of 1.5 cc. of 2-percent novocain is then given and a small amount of the same solution is injected subconjunctivally in the quadrant under examination.

An incision is then made in the bulbar conjunctiva parallel to and 10 mm. back of the limbus. The sclera is exposed and cleaned of all episcleral tissue. A point on the sclera, which we feel is nearest to where the foreign body is localized, is selected and marked. This area is then surrounded by diathermy micropins, the number depending on the length of the sclerotomy to be done. A scleral incision is then made with a Graefe knife in a radial direction from the limbus. The length of this incision will depend on the size of the foreign body.

It has been recommended by Thorpe[10] that this incision should be I or T shaped and that only the sclera should be incised with the knife, the uvea being incised with the cutting diathermy current. This seems logical but not necessary. I use a linear incision and cut through the uvea as well as the sclera with the Graefe knife. If one is fortunate, the foreign body may be seen in the vitreous by direct view when the uvea is opened and if so, it can be grasped with a forceps and removed. In the sixth case to be described later, it was my good fortune to have this happen.

If this does not occur, the foreign body is then observed through the dilated pupil with the ophthalmoscope held in one hand while the forceps, of a type similar to those devised by Thorpe[10] or Cross,[11] are held in the other hand and inserted through the scleral opening into the vitreous chamber. While observing the blades of the forceps and the foreign body with the ophthalmoscope, it is possible to grasp the foreign body and remove it through the opening in the sclera. The scleral incision is then superficially coagulated with the Lacarrere electrode; the opening is closed with interrupted fine black silk 6-0 sutures; and the conjunctival incision is closed with a running black silk suture.

The type of forceps which we have used in this procedure was similar to a Hess iris

forceps with flat corrugated tips. However, in view of Thorpe's[10] contribution on this subject, I feel that his varied and most adaptable forceps might be preferable for this type of work.

I claim no credit for the procedure although, at the time I saw the first case reported here, I had not seen or read of the procedure but followed it because it appealed to me as logical and practical. This first method was the one which was followed in the five reported cases of copper in the vitreous.

USE OF BIPLANE FLUOROSCOPE

The second method mentioned, namely, that in which a biplane fluoroscope is used, was first described by Cross.[11] He has written several articles on this subject and, in 1931, reported that up until that time he had done seven cases by this method. In one of these cases the resulting vision was 6/6. In most of his cases the foreign body was a lead shot and, in a few, a large piece of copper in the vitreous. He devised a special type of cross-action forceps which were made of No. 18 German silver wire, the ends of which were flattened and bent in the form of a circle and filed out to fit the size of shot which might be present in the eye.

Technique. A conjunctival incision is made parallel to and 8 or 10 mm. back of the limbus in the quadrant where the foreign body has been localized. The sclera is then bared and a posterior sclerotomy 6 to 8 mm. long is done at a point as near the location of the foreign body as possible. The forceps are then inserted through the incision at an angle so that their long axis corresponds to that of the wound and are then turned at right angles so that their action corresponds to the long axis of the incision. The tips of the forceps are then placed over the approximate position of the foreign body in the vitreous as located on the X-ray film. The speculum is removed and all the lights are turned out. The remainder of the operation

is carried out in darkness with the roentgenologist directing the surgeon.

USE OF OPHTHALMIC ENDOSCOPE

The third method of extraction with the ophthalmic endoscope was devised by Thorpe.[10] The instrument is a special inverted Galileon telescope, similar to those used in cystoscopy, pharyngoscopy, and so forth. It permits a view of a field 10 mm. in diameter at one inch distance. The telescope is 2.5 mm. in diameter. There is a miniature lamp, adjacent to and in front of the telescope, which is operated by a battery handle or by a cord from a rheostat. The forceps are attached behind the telescope by means of an adjustable sheath. In all, the total width of the instrument at its widest part is 6 to 6.5 mm.

Technique. It is necessary to make an incision of 8 mm. in the sclera to use this instrument. Thorpe[10] reports that he has used it successfully in five cases. Spaeth[12] also reports a certain degree of success with this instrument. I have always felt, however, that the incision necessary to use this instrument was too large and was inviting a considerable loss of vitreous, although I can see that in some cases this method might have to be resorted to in order to save the eye even though satisfactory vision might be lost.

TRANSILLUMINATION

Transillumination as described by Schultz[7] is the fourth method.

Technique. The sclera is bared as in the other procedures except over a wider area and further back so that two strong lights similar to those used in the Lancaster transilluminator can be inserted back of the globe, and gently but firmly placed against the eyeball at two different points opposite the foreign body and opposite the incision in the sclera which has been made as near to the localization of the foreign body as possible. A third and similar light is then used to illuminate the wound area. A pair of Hess

iris forceps is then used to grasp and extract the foreign body which is seen as a shadow outlined against the illuminated area behind it.

The use of this method appears logical when the foreign body cannot be seen with the ophthalmoscope. I have tried it in one case in which a large piece of copper was localized by X ray in the vitreous but could not be seen ophthalmoscopically. Unfortunately, there was a considerable amount of purulent exudate in the vitreous which interfered to some extent with the transillumination. We were unable by this method to get a definite shadow of the foreign body and were unsuccessful in its removal. The eye was lost.

LARGE NEEDLE AND SUCTION

The fifth method of removal of small nonmagnetic foreign bodies, when located in the lens, by means of a needle and suction was described by Donovan.[13]

Technique. This is done by making a small incision in the cornea just anterior to the limbus and near the 12-o'clock position. A large needle, such as that used for spinal puncture, with a rubber tube and syringe to supply suction, is then inserted through this opening and into the soft cataractous lens. The opening of the tip of this needle is kept face upward so that it can be observed by the operator and is placed underneath the foreign body in the lens at which time suction is applied and the foreign body, when small enough, is engaged in the needle and extracted. Naturally, this method is limited to children with soft lenses.

CASE REPORTS

CASE 1

History. A white woman, aged 21 years, was first examined at Wills Hospital on July 14, 1932. She stated that while operating a coil winding machine, about one hour before, a piece of fine copper wire broke off and struck her in the left eye. Visual acuity without correction was 6/9 plus in each eye.

External examination. Right eye: Entirely normal. Left eye: There was a small laceration, 1 mm. in length, in the bulbar conjunctiva on the nasal side. This was in the horizontal plane about 12 mm. from the limbus. There were no corneal abrasions or perforations. The anterior chamber was of normal depth and clear. The iris was of good color and the pupil was round, regular, and equal in size to that of the right eye. The direct and consensual light reaction, as well as the convergence reaction, were normal.

Ophthalmoscopic examination. Right eye: The media was clear and the fundus was normal in appearance. Left eye: A highly refractile, metallic-looking foreign body could be seen in the anterior vitreous. This was "S" shaped and gave the appearance of fine copper wire. It moved slightly but did not float freely. A few stringy vitreous opacities were observed posterior to the foreign body. Two small fresh circular hemorrhages could be seen well forward in the nasal portion of the retina.

Roentgenographic findings. There was an opaque foreign body in the left eye which corresponded in size, shape, and position to that seen ophthalmoscopically.

Operation. The Parker electric hand magnet was applied to the upper portion of the left globe while the foreign body was observed with the ophthalmoscope. Application of the current produced no movement whatever of the foreign body. It was then concluded that the foreign body was copper and nonmagnetic and would, therefore, have to be removed by other means.

An incision was made in the bulbar conjunctiva parallel to the limbus and 10 mm. back of it in the upper nasal quadrant. A black silk suture was inserted in the conjunctiva on either side of the incision for traction. A posterior sclerotomy, 3 to 4 mm. long, was then made radially with a Graefe knife, 10 mm. back of the limbus. An old iris forceps with worn off teeth was then inserted through the lips of the sclerotomy wound.

While observing the blades of the forceps and the foreign body with the ophthalmoscope through the dilated pupil, it was possible to grasp the foreign body and remove it through the opening in the sclera. The ophthalmoscope was held in the left hand and the forceps in the right while the assistant, by grasping the bulbar conjunctiva with fixation forceps, helped the patient fix the eye temporally. Several attempts were necessary, however, before the piece of copper was finally engaged between the blades of the forceps.

The loss of vitreous was very slight and much less than might be expected. The sclerotomy wound was then closed with one fine black silk intrascleral suture, and the conjunctiva was closed over this with a continuous silk suture.

Postoperative convalescence. The patient made a very satisfactory recovery with no postoperative hemorrhage or infection. After one week she was discharged from the hospital with visual acuity of 6/9 in the left eye with a +1.0D. sph. ⌒ +0.25D. cyl. ax. 90°. The eye was entirely quiet and the media was remarkably clear. Examination with the ophthalmoscope revealed a small white area

surrounded by small hemorrhages, well forward in the superior nasal quadrant. There was no evidence of any detachment of the retina at this time.

About two weeks later, August 10, 1932, ophthalmoscopic examination of the left eye showed a small globular detachment of the retina in the upper nasal quadrant. There was a corresponding visual field defect in the lower temporal quadrant. The detachment of the retina progressed and the patient was readmitted to Wills Hospital on August 30th. On September 1, 1932, an electrocoagulation operation was performed with the Weve needles. This failed to relieve the detachment. The operation was repeated in October, 1932. This operation was also unsuccessful.

Finally in January, 1933, a third electrocoagulation operation was done and this time the Safar needles were used. The retina remained detached, however, and the patient refused further surgery. The detachment became complete and was complicated by the development of a cataract. The eye remained quiet although it finally became blind and divergent.

CASE 2

History. A white man, aged 25 years, was first admitted to Wills Hospital on August 29, 1933, with a history of the left eye being injured by a dynamite-cap explosion three days previously. Visual acuity, with correction, was 6/6 in the right eye and 6/21 in the left.

External examination. Right eye: Entirely normal. Left eye: There was a laceration about 2 to 3 mm. in length in the corneoscleral limbus at the 9-o'clock position, with a small prolapse of iris.

Ophthalmoscopic examination. Right eye: No evidence of any pathologic condition or injury. Left eye: There was a maple-leaf, posterior cortical cataract present with an irregular square refractile metallic-looking foreign body, about 2 by 2 mm. in size, behind it. This appeared to be floating in the posterior vitreous. The vitreous was otherwise clear and the fundus healthy.

Roentgenographic findings. X ray revealed an opaque foreign body in the posterior vitreous of the shape and size described above.

Operation. It was felt that the foreign body was copper and application of the magnet failed to cause any movement of the foreign body. The same procedure was then followed as in Case 1. An irregular square piece of copper, about 2 by 2 mm. in size, was successfully extracted through a posterior sclerotomy in the superior nasal quadrant with very little loss of vitreous. In this case, however, the lips of the sclerotomy wound were sealed by means of the actual cautery after the foreign body was removed. The intrascleral and conjunctival sutures were then inserted. In this case it was also necessary to excise the prolapsed iris and to cover the limbal wound with a conjunctival flap.

Postoperative convalescence was uneventful and the patient was discharged from the hospital on

September 10, 1933. He was seen at intervals until August 22, 1934, at which time the injured left eye was entirely quiet and the lens changes were only slightly increased. Visual acuity at that time was 6/15 in the left eye, with correction. The vitreous showed one large opacity in the central portion. The fundus was healthy with no evidence of retinal detachment. The intraocular pressure was 22 mm. Hg (Schiøtz). The visual fields in each eye were normal.

CASE 3

History. A white man, aged 23 years, was first seen on November 15, 1935. He gave the history that two days previously, November 13, 1935, while winding fine copper wire on a machine, a piece of wire broke off and struck him in the left eye.

External examination. Right eye: Normal in all respects; vision, 6/7.5, without correction. Left eye: Vision 6/12—, without correction. There was a considerable amount of ciliary congestion. The pupil was not dilated and reacted sluggishly to light. A small penetrating scar could be seen in the center of the cornea. There was a small cut in the pupillary margin of the iris on the temporal side. Just behind this there was an opacity extending back through the entire lens and giving the appearance posteriorly of a typical rosettelike traumatic cataract.

Ophthalmoscopic examination. Right eye: The media was clear and the eye grounds healthy. Left eye: The corneal and lenticular changes already described were distinctly seen. The vitreous was clear and no foreign body could be seen. The eye grounds appeared to be healthy.

Roentgenographic findings. X ray revealed a small, wirelike, opaque foreign body in the anterior superior temporal quadrant of the vitreous.

Operation. On November 18, 1935, the foreign body could be seen easily with the ophthalmoscope through the dilated pupil in the anterior superior-temporal quadrant, where it had been localized by X ray. On that date the patient was admitted to Wills Hospital and the foreign body was removed by the same procedure employed in the first two cases. In this case, however, the lens was injured while attempting to engage the foreign body between the blades of the forceps.

Postoperative convalescence. On the day after the operation the lens showed a definite increase in the cataractous changes with considerable swelling of the cortex. There was marked ciliary congestion but no definite elevation of the intraocular pressure. Conservative treatment was employed until December 7, 1935, and the eye remained quite irritable. On this date a linear cataract extraction was performed. Two weeks later, December 21, 1935, the eye was much quieter and the patient was discharged from the hospital. Improvement continued and one month later the eye was entirely quiet. The vision at that time was 6/6—, with a +13D. sph.

Follow-up report. When the patient was last examined in March, 1948, the visual acuity in the

left eye was 6/9+ with a +13D. sph., and 6/5 in the right eye with +2.0D. sph. ⊃ +1.0D. cyl. ax. 180°. Both eyes were entirely quiet and the tension was 22 mm. Hg (Schiøtz) in the right eye and 19 mm. Hg in the left eye.

The left eye, externally, showed a horizontally linear perforating scar in the upper periphery of the cornea, the site of the old keratome incision which was made at the time of the linear extraction. The iris was slightly adherent to this, posteriorly, but it was not incarcerated. Some thin capsular remains, but no cortex, were present. There was a very good opening in the capsule and the vitreous appeared to be quite clear. The fundus, which could be seen easily, was entirely healthy with no evidence of any retinal detachment. Visual fields showed no gross defects in either eye.

Case 4

History. A white man, aged 22 years, was first admitted to Wills Hospital on June 2, 1943. He gave the history that while soldering 22-caliber cartridges, the day before, one of the shells exploded and a fragment struck his right eye. Visual acuity, without correction, was reduced to counting fingers on the temporal side at 1.5 meters in the right eye, and was 6/6 in the left eye.

External examination. Right eye: A through and through obliquely vertical laceration 5 mm. in length could be seen extending through the margin of the lower lid in the outer third. There was a moderate amount of photophobia and lacrimation present with considerable congestion of the bulbar conjunctiva. In the 7-o'clock meridian, beginning just 2 mm. back of the limbus and extending horizontally for approximately 5 mm., there was a perforating wound of the bulbar conjunctiva and sclera. The cornea was clear and showed no wounds or foreign bodies. Left eye: Normal in all respects.

Ophthalmoscopic examination. Right eye: The cornea and lens appeared clear. With a +10D. sph., however, an irregular glistening mass could be seen in about the middle of the vitreous. This mass was silvery yellow in color, 3 to 4 disc diameters in length, and 2 to 3 in width. There was a massive subhyaloid hemorrhage which obscured the optic disc. It began at the 11-o'clock position and extended down on the temporal side and across the midline below to about the 5-o'clock position. The upper nasal portion of the fundus was seen with a −3.0D. lens and it appeared healthy. Left eye: Media was clear and the fundus was normal in all respects.

Roentgenographic findings. The Sweet localizer revealed a large opaque foreign body which was 6.5 mm. long and 4.5 mm. wide. The center of the foreign body was 17 mm. back of the center of the cornea, 1 mm. below the horizontal plane, and 6 mm. to the nasal side of the vertical plane.

Operation. On June 2, 1943, the foreign body was removed from the right eye. The same procedure was followed as in the previous three cases. Due to the size of the foreign body, however, the

scleral incision was found to be too small. When the foreign body was grasped and pulled up to the scleral opening, it could not be extracted and dropped back into the vitreous. The sclerotomy was then enlarged and more vitreous was necessarily lost when the foreign body was finally extracted.

An additional complication occurred in the form of a massive hemorrhage which immediately followed the removal of the foreign body. The patient received typhoid-fever therapy and intramuscular penicillin in addition to local treatment. The eye never regained its normal tension and remained irritable. The patient was discharged from the hospital on June 24, 1943, with the recommendation that the injured eye should be enucleated.

Case 5

History. A white woman, aged 25 years, was first admitted to Wills Hospital on November 8, 1944. She stated that the day before, while winding coils of fine copper wire, a piece of wire broke off and struck her left eye. Visual acuity, without correction, was 6/5—2 in each eye.

External examination. Right eye: The lids, conjunctiva, and the anterior segment appeared to be entirely normal. Left eye: There was a slight amount of conjunctival congestion, lacrimation, and photophobia present. At the 8:30-o'clock position in the cornea, 2 mm. from the limbus, there was a wound which seemed to perforate into the anterior chamber. At the posterior edge of this wound one could see what appeared to be a fine piece of copper wire. The anterior chamber was normal in depth. The iris was normal in texture and the direct and consensual pupillary reactions to light were normal.

Slitlamp examination. This verified all the external findings and showed that one end of the wire was caught in the posterior lips of the corneal wound. The other end of the wire was bent almost at a right angle about 0.5 mm. from its posterior tip and this lay on the iris near its nasal periphery a little above the corneal wound. The length of the wire appeared to be 2 to 3 mm.

Ophthalmoscopic examination. This was essentially negative for both eyes, and, through the undilated pupil, no opacity could be seen in the lens of the left eye.

Roentgenographic findings. X-ray films revealed an opaque foreign body in the left eye corresponding in size, shape, and position to that seen by external and slitlamp examinations.

Operation. A small hand magnet was first applied over the left eye near the foreign body with no response. An incision into the anterior chamber was then made with a keratome, beginning 2 mm. back of the limbus and just above the position of the foreign body. This incision was then enlarged below with scissors. An iris forceps was then introduced into the anterior chamber and with this the piece of wire was engaged and removed. Some hemorrhage was encountered due to the iris be-

coming entangled, but it did not prolapse and no iridectomy was done. The iris was replaced with a spatula, pilocarpine ointment was instilled, and the eye was closed.

Postoperative convalescence. This was somewhat stormy due to the large hemorrhage in the anterior chamber which was slow in absorbing. There was some elevated intraocular pressure but this was controlled with miotics. Repeated injections of typhoid vaccine were also given. Subsequent X-ray examinations after operation failed to reveal any evidence of a foreign body. The pupil was drawn over to the nasal side and was pear-shaped, due to incarceration of the iris at the site of the paracentesis.

The patient was discharged from the hospital on December 1, 1944. The eye continued to improve and on January 2, 1945, the patient returned to work with 6/6—1 visual acuity, without correction, in her injured left eye. She had a slight flare-up in April, 1945, but this was quickly relieved by local treatment and the patient has had no trouble since. Today the vision in the left eye remains 6/6—2, without correction, and the eye is entirely quiet with normal intraocular pressure. The pupil is still distorted as described, and there are some lens changes which have remained localized in the nasal periphery. These appear to be limited to the anterior capsule and are apparently organized hemorrhage and pigment. The uninjured right eye has been and remains entirely free of any irritation, with normal vision without correction.

CASE 6

History. A white youth, aged 18 years, was admitted to the Wills Hospital on April 12, 1948. Five days previously he had been tampering with a defective dynamite cap which suddenly exploded, and something struck him in the right eye causing a slight laceration of the right upper lid with a small amount of bleeding. Visual acuity at this time, without correction, was 6/6 in the right eye and 6/12 in the left eye.

External examination. The right eye revealed a healed laceration in the upper lid near the inner margin and, under the nasal bulbar conjunctiva, there was considerable hemorrhage which was undergoing absorption. No definite evidence of a perforating wound in the sclera could be seen at that time. The eye otherwise appeared to be quiet and the cornea was entirely clear. The anterior chamber was normal in depth, and the pupil was moderately dilated. The iris was healthy in color with no evidence of injury. Left eye: Entirely normal.

Ophthalmoscopic examination. Right eye: The cornea and lens were entirely clear. The vitreous showed a few stringy opacities. In the lower nasal periphery, just back of the equator, there was a large mass of exudate which extended from the retina into the vitreous. In the center of this, near the anterior edge, there was a highly refractile metallic-looking foreign body. This was somewhat square in shape with slightly irregular edges and

appeared to be slightly larger than 1 disc diameter in size.

Anterior to the foreign body, and slightly more to the midline and below, there was another mass of exudate which extended as far forward as one could see. There was no free hemorrhage present and no definite tear could be seen in the retina. There was no evidence of any retinal detachment. The optic disc and macula both appeared to be entirely normal. Left eye: The media was clear and the eye grounds appeared entirely healthy.

Roentgenographic findings. X-ray films showed a small opaque foreign body, the density of which suggested copper, in the right eye. This was localized 19 mm. back from the center of the cornea, 7.5 mm. below the horizontal plane, and 9 mm. to the nasal side of the vertical axis. The approximate size of the foreign body was 1 to 1.5 mm. in diameter.

Operation. The patient was prepared for operation in the usual manner. The hand magnet was then applied while viewing the foreign body with the ophthalmoscope. No response was noted. In view of this, we felt quite certain we were dealing with a piece of copper in the right eye. We decided to follow the same procedure in this case as we had in the previous ones.

The procedure was exactly the same except that, in this case, we were a little more careful in our localization of the foreign body, since it appeared to be lying close to the retina. We tried to localize it in the same manner as we have been localizing retinal tears in retinal detachments. In doing this, we had our assistant hold the Arruga spoon between the exposed sclera and the bulbar conjunctiva in the lower nasal quadrant while we focused on the foreign body with the ophthalmoscope. This was done with the operating room in darkness.

The assistant observed the light of the ophthalmoscope as it was transilluminated through the sclera and, when we were accurately focused on the foreign body, he marked the sclera with gentian violet at the point where the light was most concentrated. The assistant also exerted pressure on the sclera at this point with a squint hook while we observed the foreign body with the ophthalmoscope, and we could see the foreign body move forward each time the sclera was indented with the squint hook. After the posterior sclerotomy had been made, a bead of vitreous presented through the lips of the scleral incision. In this vitreous bead could be seen a small highly refractile foreign body which we immediately removed with a pair of small forceps.

This foreign body proved to be a piece of copper of the same size and shape as that which we had seen in the eye and which was shown on the X-ray plates. We then looked into the eye again with the ophthalmoscope and could no longer see the refractile body. The wound was closed in the manner as described in the other cases.

This patient made an uneventful recovery and, at the time of his discharge from the hospital, which

was about three weeks after the removal of the foreign body, the eye was quiet. The retina was in good position and the vision in the injured eye was 6/9 with correction. It has now been over one year since the patient's discharge from the hospital, and he has been seen at intervals since then. At the present time, the vision in the injured eye, with correction, remains 6/9+, and there is no evidence of any retinal detachment.

SUMMARY

Six cases of intraocular copper are presented. Nearly 16, 15, and 13 years, respectively, have elapsed since operation in the first three cases. In Cases 4 and 5 it has been over three years since operation. Case 6 has now been under observation for over one year.

In 5 of the cases the copper was in the vitreous and in one it was in the anterior chamber. The first, third, and fifth cases were similar in that they were all injured on coil winding machines at the same plant. The type of foreign body in these 3 cases was a fine piece of copper wire. The second and sixth cases were injured by a dynamite-cap explosion. The fourth case was injured by an exploding 22-caliber cartridge.

A technique is described for the removal of nonmagnetic foreign bodies from the vitreous and the anterior chamber, respectively.

The first 4 cases, all with copper in the vitreous, were operated by means of a posterior sclerotomy, through the lips of which a small capsule forceps was inserted. While looking with the ophthalmoscope through the dilated pupil, the operator was able to grasp the foreign body in the vitreous and extract it through the sclerotomy opening. In the first case the scleral opening was closed with interrupted black silk sutures with no cauterization. In the other 3 cases the same method was employed but the sclera was coagulated around the incision with diathermy before suturing.

The first case made an uneventful recovery and the vision was normal for five weeks following the operation. At the end of this time a retinal detachment was observed. This became more marked and, approximately two months after the original accident, a retinal detachment operation was done with the Weve needles. This was unsuccessful and two more retinal detachment operations were performed, Safar pins being employed at the last operation. These were all unsuccessful. Today, more than 15 years later, the patient's injured eye is divergent, has a complicated cataract, and no light perception.

The second case made an uneventful recovery. In spite of the fact that he had a partial posterior cortical cataract, from the time he was first seen, there has been no material progress in the lens changes and now, almost 15 years after the injury, he has useful vision, 6/15 with correction. There was no evidence of any retinal detachment at any time and the visual field has remained full.

The third case showed more reaction following operation than the first two cases. The partial cataract which was present before operation became complete shortly after this and a linear extraction was necessary. Following the cataract extraction, the patient made an uneventful recovery and has had no trouble since. Today, 13 years after the injury, the eye is entirely quiet with normal tension. The vitreous is clear and the fundus is healthy with no evidence of detachment. The visual field is full and the visual acuity of the injured left eye is 6/9 plus with +13D. sph.

The fourth case offered a poor prognosis due to the very large foreign body and the massive preretinal hemorrhage which was present when the patient was first seen. A considerable amount of vitreous was lost and more hemorrhage occurred at the time of the extraction of the foreign body. This hemorrhage persisted and eventually the eyeball became phthisical. Enucleation of this eye was advised.

The fifth case showed the copper wire to be present in the anterior chamber. This was removed by means of a paracentesis made with a keratome and enlarged with

scissors. The foreign body was then grasped with iris forceps and withdrawn. However, the iris became entangled and had to be replaced through the wound. This resulted in some incarceration but no prolapse of the iris. The pupil became pear-shaped and drawn to the nasal side. A localized opacity still remains on the nasal side of the anterior lens capsule. The media are otherwise clear, the fundus healthy, and both eyes are entirely quiet. The visual acuity without correction today is 6/5 in the right eye and 6/6 — in the injured left eye.

The sixth and last case reported was one in which the nonmagnetic foreign body was localized in the vitreous, and the same procedure was followed as in the other cases of nonmagnetic foreign bodies in the vitreous. However, in this case we were much more fortunate than in the others because, after the sclerotomy opening had been made, a bead of vitreous presented with the piece of copper glistening in its center. This was then extracted with forceps and the necessity for going any deeper into the vitreous was avoided. The scleral wound and conjunctiva were then closed in the same manner as in the other cases.

Conclusion

I feel that the results obtained in the 5 reported cases of copper in the vitreous, justify the technique followed. However, a special type of forceps, such as a modification of the alligator forceps used by otologists, or a smaller and stronger forceps similar to those of Thorpe,[10] but with the handles lower down, might aid in grasping and holding the foreign body.

I recognize the fact that if the lens is too opaque for one to see the foreign body, the procedure described cannot be employed. However, since removal of the cataractous lens would be indicated anyway, this could be done first and the technique described could then be carried out. I feel that, when it is possible to see the foreign body ophthalmoscopically, the method described provides the best procedure for the average ophthalmic surgeon successfully to remove nonmagnetic intraocular foreign bodies.

Of course, when the vitreous is very cloudy, due to hemorrhage, the method of choice might be the use of the biplane fluoroscope as described by Cross.[11] This, however, is not without danger and there are very few of these instruments available. Also, small pieces of metal, particularly copper, are almost impossible to see with this method. Indeed, most of the cases which Cross[11] has reported were lead shot or large pieces of copper in the vitreous.

The method here described requires patience as well as perseverance throughout, but especially in approaching and grasping the foreign body with the forceps. It must be realized that the forceps, as well as the foreign body, are magnified by the ophthalmoscope. Except in cases of very large-sized foreign bodies, the sclerotomy opening need not be large. All scleral openings should be electrocoagulated with a small amount of current such as is used with a Lacarrere instrument. I also like to touch the edges of the scleral incision with 50-percent trichloracetic acid or 50-percent phenol just before closing the conjunctiva, as suggested by Stieren.[14]

It is now realized that, in the first case, the eye should have been saved. The retinal tear made by the posterior sclerotomy should have been sealed off and the detachment could have been prevented. Failure to do this was the result of a lack of sufficient knowledge about the method for, and the importance of, closing retinal tears 16 years ago.

In Cases 2, 3, and 5, the results were as satisfactory as one could expect from such drastic surgery. Case 4 was considered very unfavorable when first seen due to the large size of the foreign body, and the massive preretinal hemorrhage. However, a larger sclerotomy might have been done first and the foreign body could have been more easily extracted with less trauma. It is realized in retrospect that an iridectomy should

have been done in the fifth case, thereby avoiding the incarceration of the iris. The sixth case illustrates the importance of a very accurate localization of the foreign body and the advantage of making the sclerotomy as near it as possible.

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HISTORICAL MINIATURE

Egyptian Ophthalmology

We know from the writings of Clemens Alexandrinus (200 A.D.) that the first 36 of the 42 cannonical books of the Egyptian priests contained their entire wisdom and the last 6 were medical. They dealt with the organization of the body, diseases, instruments, drugs, the eye, and gynecology. It is noteworthy that a separate book was devoted to the eye. The primary document that has come down to us is the papyrus (1500 B.C.) which Ebers found at Thebes in 1872. It is chiefly a treatise on the management of disease. There is no indication that medicine was divided into specialized disciplines.

The theoretic knowledge of the ancient Egyptians was meager, despite their extensive experience in dissection and embalming, but their therapeutics was not to be despised. They knew the action of castor oil, the use of pomegranate bark for tapeworm, and of treatment by inhalation. The section of the Ebers's papyrus on ocular disease begins with a description of the commonest eye disease, conjunctivorrhea which is characterized by three striking manifestations: redness, exudation, and swelling. They recognized chronic trachoma and recommended a preparation that contained verdigris, myrrh, onion, and gazelle dung. It was to be brushed into the eye with the feather of a vulture.

Hirschberg, Graefe-Saemisch Handbuch.

EVALUATION OF ANISEIKONIC CASE REPORTS*

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The new space eikonometers make it practical for an ophthalmologist to measure aniseikonia without the necessity of a technician. The time required in testing is less than 15 minutes. Aniseikonia can be ruled out in 5 minutes.

There will be larger series of patients studied, and new evaluations of aniseikonia made. Although most of this work will be done by those already acquainted with aniseikonia, there are some who will report cases for the first time. Case reports in the past have elicited criticism on various points to be discussed in this paper.

To illustrate the difficulties in evaluating aniseikonic case reports recorded in the past, this paper describes 100 of the first patients treated with aniseikonic spectacles by the Washington University aniseikonic clinic. The patients were first seen in 1939 and 1940, and responded to a questionnaire in August, 1944. Thirty reported no improvement, 32 moderate improvement, and 38 complete relief. Twenty-six of the 70 reportedly improved have returned more recently for review and received new aniseikonic spectacles. All were private patients of ophthalmologists, and only 5 percent came from a distance of less than 50 miles.

INCOMPLETENESS OF DATA

Criticism of most case reports published to date applies to the present series, and is based on incompleteness of the following data:

1. A careful history, reviewing all the systems. General medical studies when indicated. At least the physician's opinion as to the patient's psychiatric state. Duration of symptoms.

2. Occupation, visual habits.

3. Keratometer readings.

4. Stereoscopic acuity.

5. Progress notes.

6. Sensitivity or precision of the patient.

7. The effect of change of prescription alone.

8. Meridional aniseikonic measurements have not been taken nor has the influence of oblique astigmatism on the prognosis been considered. The old ophthalmo-eikonometer was incomplete in this respect.

Data probably faulty were used when aniseikonia measured at 13 inches was not found at 15 feet. This aniseikonia for near is possibly due to physiologic exophoria, decreased sensitivity on the ophthalmo-eikonometer at near, the effect of unequal accommodation, and proprioceptive factors. This difference is not found in the space eikonometer.[1] Many prescriptions have been given for aniseikonia found only at 13 inches, and are reportedly beneficial. Three such cases appear among the improved group in this series.

SERIES OF CASES STUDIED

Most of the patients in this series came from a distance, and, to save money and time, prescriptions were given on the basis of a single examination. In difficult cases, this is unwise even in ordinary refraction.

Five of the unimproved patients reported in the follow up letter that diagnoses had been made: encephalitis, sinusitis, carotid sinus syndrome, uremia and nervous exhaustion. Symptoms in aniseikonia are not pathognomonic, but should be carefully considered. If headache is not related to use of the eyes, it is not aniseikonic. Records should state whether eyestrain, headache, or nausea follows reading, watching small moving objects, riding a vehicle, or seeing the movies.

Aniseikonic symptoms are rarely of recent onset, unless induced by new glasses. Visual acuity is usually above normal with glasses, and there may be anisometropia or unequal astigmatism. All patients with oblique astigmatism have oblique aniseikonia. History of relief upon monocular blurring or occlusion is diagnostic of a binocular anomaly. Photophobia is a common complaint in aniseikonia.

Just as small errors of astigmatism may not annoy a laboring man, aniseikonia does not always cause symptoms. Aniseikonic glasses should not be placed on every patient until the costs come down within reason. Even in the presence of low stereoscopic acuity, if the patient is comfortable, aniseikonic glasses are not indicated. If the patient is a surgeon and cannot get his hemostat near a bleeder, an exception may be made.

OCCUPATIONAL GROUPS

Aniseikonia is symptomatic in persons in certain occupational groups who make extraordinary demands upon their eyes. One must admit that the same occupational groups are notoriously subject to neurosis. In the present series, the occupation could only be obtained in some cases from the correspondence. Among those completely relieved were: 12 housewives, 3 students, 2 bank presidents, 2 attorneys, 1 physician, 1 writer, 1 treasurer, 1 minister, 1 insurance manager, 1 hardware dealer, 1 stenographer, 1 soldier, 1 navy officer, 1 oil manager, and 1 war worker.

Those moderately improved included 4 housewives, 1 oil engineer, 1 assessor, 1 sanitary engineer, 1 nurse, 1 physician, 1 stenographer, 1 brewer, and 1 navy-yard worker. Those unimproved included 9 housewives, 2 physicians, 1 minister, 1 sailor, and 1 radio engineer.

TESTING DEPTH PERCEPTION

Patients with uncorrected aniseikonia compensate by using monocular clues for space perception and by suppressing binocular vision. Therefore, stereoscopic acuity should be recorded in each case. This is done automatically in the space eikonometer by recording the sensitivity to changes in the image size. Space-eikonometer tests will show defective depth perception in many found normal by other tests in use. If stereopsis is so defective that tests on this instrument are impossible, a few periods of orthoptic training are indicated. Usually, the sensitivity improves remarkably after brief daily tests on the instrument.

Ordinary refraction patients may go for 5 years or more without a change in prescription or even a frame adjustment. Aniseikonic patients soon learn that a change of one millimeter in lens to cornea distance will cause recurrence of symptoms, and are constantly returning for adjustment. It is almost certain that patients who do not return for recheck in 2 years are not suffering from aniseikonia. Of the present series, only 26 returned even once since August, 1944. All 26 were among the improved group. It may be that some patients returned to their ophthalmologist instead of the clinic. At any rate, no other progress notes were found in the records.

SENSITIVITY TO SMALL DIFFERENCES

The sensitivity of the patient to small differences in measuring aniseikonia is very important in evaluating a case, and should be recorded. On the ophthalmo-eikonometer, sensitivity has no relation to stereopsis. However, if the prescription is: O.S., 0.75 percent, and the sensitivity is plus or minus 1.00 percent, the patient will obviously get an imperfect correction. After wearing the rough correction for a month, the sensitivity improves so that a more exact prescription can be made. If it does not improve, the patient must be suppressing, and probably needs orthoptic training.

The sensitivity on the ophthalmo-eikonometer is between 0.50 and 0.25 percent difference in image size of the two ocular

systems. On the space eikonometer it is commonly 0.25 percent on patients, and as high as 0.05 percent in trained observers. The space eikonometer target is so sensitive that it is made asymmetrical by introduction of a −0.12D. cyl. ax. 90° from the trial case before one eye.

Balancing aniseikonia will not overcome mistakes in ordinary refraction. A patient may not have measurable aniseikonia with the proper spectacles, but an incorrect prescription will certainly produce it. It is the experience of all aniseikonic clinics that the majority of referred patients are made comfortable by a quarter diopter change in cylinder, a slight change in axis, introduction of prism, and so forth.

On the other hand, aniseikonia can be balanced in anisometropia by undercorrection. For instance: O.D., +1.0D. sph., O.S., +8.0D. sph., there is likely to be marked aniseikonia with the full correction. However, +1.0D. sph., O.U., may neutralize it. If aniseikonia is thus neutralized, the patient may be relieved—or, more commonly, may suppress. One cannot depend, however, on aniseikonia being proportional to anisometropia.

WEARING OF ANISEIKONIC GLASSES

Patients should not be considered suffering from aniseikonia until it has been demonstrated that they cannot wear their full prescription after a month's continuous trial. Patients should not be permitted to remove the glasses except for sleep. Perhaps medication will be indicated in some patients.

Two patients in this series stated that it required a year to get used to their aniseikonic glasses. This lengthy period is probably due to wearing glasses part time only.

It is known that glasses change the accommodation-convergence ratio, change the habitual accommodation level upon fixing at various distances (one's eyes are seldom optically focused upon the object of fixation), and also cause varying excursions in the reading and other positions of gaze.

In anisometropia, inducted vertical phoria in the reading position is always found. Since it is known that aniseikonia is an anomaly of binocular vision, and that eye movements are unquestionably involved, the matter of habit must be considered. The patient may be unable to adapt to two sets of conditions for accommodation and ocular movements, when by habit, he could adapt to one.

It is believed unlikely that any patient will get relief of aniseikonia by wearing glasses for reading only, or part time only. Of the 9 patients in this series who used glasses for reading only, only partial relief of symptoms was reported by 6.

When first putting on glasses correcting his aniseikonia, the patient notices space distortion. Table tops tilt, and buildings lean. This is diagnostic of aniseikonia, and should disappear in a few days if the glasses are correct and are worn constantly. Originally, patients were given a partial correction at first to avoid this effect, measured on the leaf room or tilting table. This has been found unnecessary.

OBLIQUE ANISEIKONIA

Case reports in the past cannot be properly evaluated because, with few exceptions,[2] oblique aniseikonia has not been considered. Patients have not even been classified as to the possible influence on the results of the oblique astigmatism present.

If one considers about 2.0D. of astigmatism of axis 15 degrees or more as likely to cause complaint, 8 of the unimproved patients and 15 of the improved had a right to continued complaint. As none of the records show whether astigmatism was measured monocularly or binocularly, it is unknown whether the axes prescribed in any case corresponded to the position of action of the eyes in fusion.

All patients with unequal corneal astigma-

tism have proportional aniseikonia, unless by rare coincidence it is neutralized by the crystalline lens, the shape of the posterior segment, or the dispersion of the retinal elements.[3, 4]

CRITERIA OF CLASSIFICATION

Each of the 100 patients in the present series was classified as to the probability of complaint from aniseikonia, according to the following criteria: anisometropia (particularly astigmatic), symptoms of photophobia, eyestrain on reading, headache or eyestrain on driving a car or riding on a train, apparent benefit from wearing the aniseikonic prescription, returns for retesting or adjustment, visual acuity with glasses, presence of oblique astigmatism, phorias, and prism.

Of the 30 patients reportedly unimproved, 11 probably were suffering from aniseikonia according to the above criteria. Most of the group simply reported the glasses did not help, but 8 were contentious and belligerent. Of the 70 patients reportedly improved, 46 were probably aniseikonic according to the above criteria, and 24 were atypical. Of the atypical cases, 21 were possibly improved due to the change in refraction alone, since no test period without anisekonia was prac-

tical. Among the improved patients were: 4 who received vertical prisms, 1 horizontal, and 1 both. Among the unimproved were 4 who received vertical prisms.

Of the 46 probably aniseikonic patients, 19 made return visits after 1944 for new prescriptions. Of the 24 patients not considered typical, 7 returned for new prescriptions. Of the 46 patients considered aniseikonic, 28 reported complete relief and 18 partial relief. Of the 24 not considered typical, 13 reported complete relief, and 11 partial. Of those not considered typical, 6 used their glasses for reading only; and of those probably aniseikonic 3 used their glasses for reading only.

Of the 70 improved patients, only 12 had no significant refractive change. Of the 12, 4 reported complete relief, and 8 partial relief. Three of the latter were in the group not typically aniseikonic.

SUMMARY

One hundred of the first patients treated by the Washington University aniseikonic clinic are reviewed. Suggestions are made to improve recording of case reports for the purpose of future evaluation of aniseikonia.

640 South Kingshighway (10).

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NOTES, CASES, INSTRUMENTS

A SIMPLIFIED METHOD OF ENUCLEATION WITH A MOTILITY IMPLANT*

FRANK W. NEWELL, M.D., ROBERT W. ZELLER, M.D., AND HARRY S. KUPER-SMITH, M.D.
Chicago, Illinois

Recently ocular implants, which transmit motility to an artificial eye by means of a connecting bar or peg have been described. Usually the operative procedure involves isolating and individually attaching the rectus muscles to the implant. We wish to report a simple surgical method which has yielded excellent results at Cook County Hospital in both primary and delayed implantation.
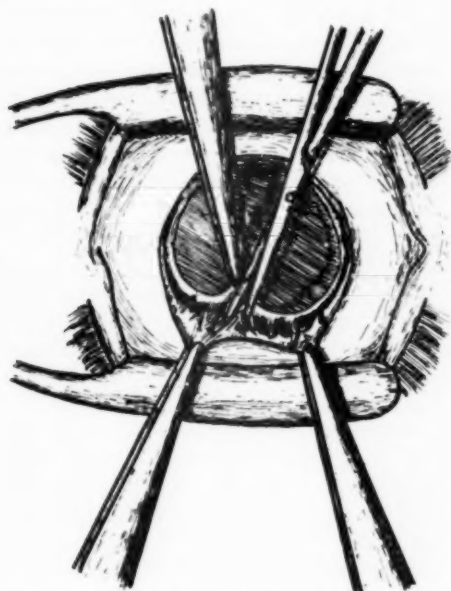
Fig. 1 (Newell, Zeller, and Kupersmith). Dissection of Tenon's capsule from conjunctiva.

Cutler's universal (tantalum mesh) implant is used. Prior to surgery 4-0 chromic catgut sutures are placed in each quadrant of the mesh 3 mm. from the anterior margin.

The conjunctiva is incised at the limbus in the usual manner. Tenon's capsule is bluntly undermined in the oblique quadrants. The rectus muscles are cut from the

Fig. 2 (Newell, Zeller, and Kupersmith). Preplaced sutures are passed through Tenon's capsule and tied.

globe and allowed to retract. After enucleation Tenon's capsule is separated from the conjunctiva for a distance of 3 mm. (fig. 1).

The implant is then placed within Tenon's capsule and the preplaced sutures are passed through the edge of the capsule and tied (fig. 2). No attempt is made to attach individual muscles and, although they retract, their action is exerted through the capsule. The conjunctiva is attached to the anterior edge of the mesh with six interrupted black silk sutures (fig. 3). A conformer is placed in position immediately and a pressure dressing is applied. Motility is good immediately and improves as the capsule shrinks.

The technique has been equally satisfactory with immediate and delayed implanta-
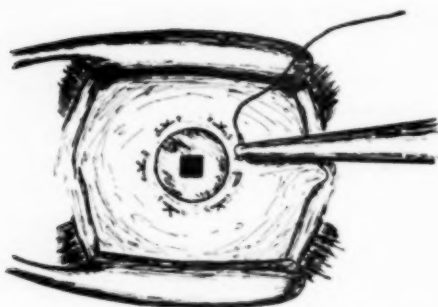
Fig. 3 (Newell, Zeller, and Kupersmith). The conjunctiva is closed with interrupted black silk sutures.

tion. Excursion of the artificial eye is as good, or better, as with the usual operation and the postoperative reaction is minimal.

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ALNICO-5 PERMANENT HAND MAGNET*

For the removal of magnetic intra-ocular foreign bodies

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In November, 1945, Brodsky[†] gave an interesting historical review on the use of magnets in ophthalmology and reported on a new permanent hand magnet which he described as belonging to the "alnico" family of magnetizable alloys. In addition to the magnet he used soft iron caps, some with straight—others with angular—points for slipping on either end. This simplification over the electromagnet with at least three separate parts is still not completely satis-

† Brodsky, B. S.: New permanent hand magnet in the light of present day magnet operation methods. Am. J. Ophth., 28:1245-1251 (Nov.) 1945.

factory because of the ease with which the caps may be lost or misplaced. The addition of soft iron caps to the end of the magnet results in an increase in the reluctance with an appreciable loss of flux due to the air gap no matter how small it may be between the two metals.

The desire for a single unit hand magnet of the permanent type suitable for insertion directly into the globe, if need be, led to the design shown in Figure 1, using the product developed by the General Electric Company about a decade ago known as Alnico-5. This is an alloy of 8 parts aluminum, 14 parts nickel, 24 parts cobalt, 3 parts copper, and the balance iron. This particular magnet material differs from Brodsky's magnet in having the addition of copper and is about twice as strong. It is interesting to note that, of all metals in the alloy, iron is the only one capable of separate magnetization, although cobalt is weakly so under the proper conditions. The maximum induction of Alnico-5 is 15,700 gausses and the coercive force is 575 oersteds. A comparison of Alnico-5, which has a higher external energy than any other alnico or other available permanent magnet material known today, and other magnets is shown in Table 1.

TABLE 1

COMPARISON OF VARIOUS TYPES OF MAGNETS

Magnet Material	Minimal Residual Induction Br (Gausses)	Minimal Coercive Force H (Oersteds)	Minimal External Energy (BdHd) max.
Carbon steel	8,600	48	180,000
Chromium steel	9,000	63	290,000
36% Cobalt steel	9,000	210	935,000
Alnico 1	7,100	400	1,300,000
Alnico 4	5,200	700	1,200,000
Alnico 5	12,000	575	4,500,000

The first model of the magnet is much smaller and lighter, weighing approximately 5 gm., than conventional hand magnets and has about 7 times the magnetic energy value. This value per unit weight is over 17 times that of carbon steel. This particular type of alnico is best cast to the shape finally desired

although the point of the second model of the magnet was satisfactorily ground to shape without loss of flux. Other alnicos of less energy value can be sintered. In the handling of these small cast magnets, care must be taken not to drop or otherwise mishandle them because of the danger of chipping or fracturing. This is because, in the cooling of these magnets, large crystals of the metal orient themselves at the corners or edges.

Once magnetized this magnet will lose only a fraction of 1 percent of its energy per year. It can be remagnetized readily if occasion demands. After the alloy has been removed from the field of the magnetizer, but kept in a closed circuit (soft-iron keeper across its poles), it will have the maximum residual induction it can maintain without outside influence. If the keeper is removed (open-air circuited) the magnet will become partially demagnetized and the value of the magnetic flux density will drop to a lower point on the demagnetization curve. This value will remain constant until the magnet is subjected to further adverse effects such as heat, vibration or impact, stray magnetic fields, or changes in the external magnetic circuit such as an increase in the air gap length.

Electromagnets of various composition, construction, and weight have been in use for many years in the removal of intraocular pieces of steel. While mobilization of the foreign body and delivery to the operative site is comparatively easy using the powerful flux of the electromagnet, the actual removal of the object from the eye with such a force, particularly in the anterior segment, renders the delicate tissues of the iris and ciliary body liable to tearing and even prolapse. It has been observed frequently that the electromagnet would bring the body just to the site only to have it slip back toward its original position when the current was turned off. After several such attempts at removal, the instrument would become too hot to handle with bare hands and the use of a towel or two would make the entire pro-

cedure too cumbersome for practical use. Allowing the instrument to cool is time consuming and serves to unnerve an already anxious patient. Even with the magnet in position and turned on, the use of additional contact instrumental aid does not help matters because of the almost certain blind probing that ensues.

CASE REPORTS

CASE 1

History. Mr. E. L. H., a farmer from middle Georgia, was seen in the office about 6 hours after receiving injury to the right eye on April 10, 1948. He stated that he had been hammering on a nut and bolt attachment of the cultivator to his tractor when suddenly vision in the right eye became very blurred. He experienced no pain but knew that something flew into his eye.

Examination revealed a 2-mm. linear wound perpendicular to the limbus at the 7-o'clock position and extending partly into the cornea. There was a droplet or two of vitreous extruding from the wound, the lips of which were in apposition. The anterior chamber was still formed. Vision was: R.E., fingers at 10 feet; L.E., 20/20. Due to the presence of vitreous floaters the fundus was not observed.

Treatment. The patient denied any past history of immunization of any kind. He was accordingly given 1,500 units of tetanus antitoxin and admitted to the hospital where he received a total of 650,000 units of penicillin G intramuscularly.

The right pupil was dilated with 1-percent atropine sulfate and with the +15 lens of the ophthalmoscope a shiny angular object almost filling the pupil was seen toward the nasal side and was found to move with the observer.

The following day X-ray localization studies, using Sweet's technique, were made showing an opaque foreign body 2 by 1 by 1 mm. located 7 mm. in back of the center of the cornea, 2 mm. to the nasal side of the vertical corneal plane, and 0.5 mm. below
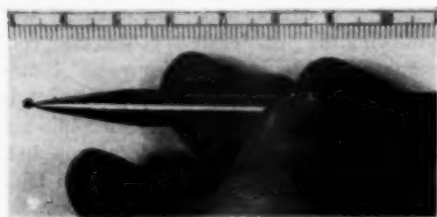
Fig. 1 (Lineback and Crawford). First model of Alnico-5 permanent hand magnet showing the foreign body removed in Case 1 attached to tip.

the horizontal plane. This placed it just behind the lens. By use of the Berman locator the foreign body was found to be magnetic.

Operation. In the office about 42 hours after injury, the patient was prepared for operation. Local anesthesia was 2-percent butyn. The patient coöperated splendidly so that only minimal use of the fixation forceps was necessary.

A conjunctival flap was made from the 6- to the 9-o'clock positions, 3 mm. from the limbus, undermined and laid back over the cornea. A wide-angled keratome was inserted just at the limbus in the site of the original wound and into the anterior chamber about 3 mm. The Lancaster hand electromagnet was then brought up to the incision after the keratome was removed. When the magnet was turned on a tugging and bulging was seen in the lower portion of the iris but, in spite of repeated attempts, the piece of steel could not be delivered. The patient experienced moderate pain at this point.

While waiting for the electromagnet to cool, the slim-nosed hand magnet was inserted 0.5 cm. into the incision and anterior chamber. Upon slow and cautious withdrawal from the globe the foreign body was found attached to the inferior surface (fig. 1).

The conjunctival flap was then reposited in its original position, penicillin ophthalmic ointment was placed in the conjunctival sac, and an eye pad was applied with moderate pressure. When anesthetization was completed the entire procedure took only 5 minutes. After undermining the flap and before the keratome incision is made, it is advisable to place a drop or two of 2-percent butyn on the limbus before proceeding.

Course. The following day the anterior chamber was found reformed and the pupil was dilated to perfect roundness by using the 10-percent emulsion of neosynephrin hydrochloride. A week after the removal of the foreign body, vision was R.E., 20/200, without glasses. He was then put on iodides orally and 2-percent dionin (ethyl morphine) drops to the right eye twice daily. One week later (2 weeks after his accident) vision was: R.E., 20/25−1 with a −1.75D. sph. ◯ −0.5D. cyl. ax. 180°. One month after the accident vision was: R.E., 20/50 without glasses and with a −1.25D. sph. was 20/20. Four months after his accident vision was: R.E., 20/20, without glasses; L.E., 20/15−.

Comment. After the success with the first model magnet, it was decided to design one still more powerful yet not too large to be used by hand. Alnico-5 is so hard and brittle that it is not readily ground to dimensions, and heating the alloy to grind it destroys most of the magnetic properties; however, it was decided to go ahead anyway with cold grinding and see how it would affect the resulting magnet. This ended with Model 2 as shown in Figure 2. It is 9 mm. in diameter, 11.5 cm. long, and weighs 30 gm. It starts vibrations in an object at 60 mm. At 55 mm. it raises the object and at 53 mm. holds it vertically without vibrations. This model arrived just before Case 2.

Fig. 2 (Lineback and Crawford). Second model of Alnico-5 magnet showing foreign body removed in Case 2 being held vertically without vibration at 53 mm.

CASE 2

History. Mr. E. H. C. was operating a punch drill on May 21, 1948, when the bit shattered and a piece of it entered his right eye, nasally. There was profuse bleeding and much pain. He was seen in the office within one-half hour after his accident.

Examination revealed a large subconjunctival hemorrhage in the inner canthus and a small 0.5-mm. linear wound, 2 mm. out from the limbus at the 3-o'clock position. Nothing was seen in the depths of the wound even with the binocular loop.

An X-ray film was not taken at this time for the desire to try the new magnet was great. It was brought up to the tiny wound after a drop or two of 0.5-percent pontocaine was first placed in the conjunctival sac. Before the point was within an inch of the wound the foreign body appeared, but it was not brought completely out because of a "hook" at the distal end which caught in the conjunctiva (fig. 3.). This was divided and the body was removed easily.

An X-ray film was then taken showing no more opaque bodies. Intramuscular injection of Omnadin* was given, and the right pupil was dilated with 1-percent atropine. Funduscopic examination revealed no lens or vitreous changes or hemorrhages intraocularly.

Five weeks after his injury his vision was: R.E., 20/40, without glasses and with a 0.50D. cyl. ax. 90° was 20/20; L.E., 20/15, without glasses.

SUMMARY

Two cases of magnetic removal of an intraocular foreign body using the new Alnico-5 permanent hand magnet are reported. The advantages of such a magnet are emphasized:

1. Its light weight and small size as compared with the electromagnet result in ease of handling.

* Omnadin—brand of Prolipin, product of Winthrop Chemical Co., Inc.

Fig. 3 (Lineback and Crawford). Showing "hook" on distal end of foreign body removed in Case 2. This "hook" caught in the bulbar conjunctiva preventing the removal of the entire foreign body by the magnet.

2. Its increased magnetic energy over conventional permanent type hand magnets.

3. Its comparative ease of sterilization.

4. Its use to shorten operating time in stubborn cases when the electromagnet fails to deliver the foreign body.

5. The fact that it is in one piece and its portability allows it to be used by the physician anywhere, particularly when no current is available for the large electromagnets.

Where possible pre- and postoperative X-ray studies should be made; the former to localize accurately the foreign body and to determine the position of the removal incision, and the latter to prove, if a medicolegal question ever came up, that the body actually was removed. It is possible, although not likely, that a patient would get another foreign body in the same eye a few days later and claim that the first one had not been removed completely.

Once localized and a choice of incision having been made, it is essential that all conjunctiva surrounding the operative site be dissected away cleanly so that there is nothing for the body to catch in when it is removed from the depths of the globe.

It is hoped and expected that, with accurate localization of the intraocular foreign body, careful selection of the site of the incision to remove it, and adequate exposure to prevent catching in the conjunctiva, this magnet can be used in place of the more cumbersome electromagnets.

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REFRACTION CLINIC*

DISCUSSION

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A 38-year-old housewife, who is complaining of blurred vision and who has recently been given glasses which she cannot wear, appears for examination. She states that she occasionally has headaches, which do not suggest an ocular basis, and, during these periods, she turns to her old glasses which are 15 years old. Her new glasses make her nauseated and she is unable to wear them without discomfort. The patient states that she does not read very much.

Refractive findings. Examination reveals the following: O.D., 20/400 with a −3.5D. sph. ◡ −3.75D. cyl. ax. 180° = 20/30, slow; O.S., 20/400 with a −3.0D. sph. ◡ −3.5D. cyl. ax. 180° = 20/30, slow.

Phorias. Distance: 3Δ exophoria; vertical orthophoria. Near: 12Δ exophoria; vertical orthophoria.

Prescription of 15-year-old glasses: O.D., −1.25D. cyl. ax. 180°; O.S., −1.5D. cyl. ax. 180°.

Prescription of recent glasses: O.D., −3.0D. sph. ◡ −3.75D. cyl. ax. 180°; O.S., −3.0D. sph. ◡ −3.75D. cyl. ax. 180°.

DISCUSSION

The fact that this patient has gone so many years without changing her glasses, coupled with the fact that she has worn a decided undercorrection, immediately tends to indicate that we are dealing with a person who is not very critical about keenness of vision. Also, the fact that her new glasses which are closer to her refractive error produce symptoms may well be due to several factors.

1. It may be that her accommodation is not

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well developed and, therefore, the use of accommodation between infinity and her near point demanded by the full correction of her myopia is the cause of the difficulty.

2. It may be due to the full correction of the "with the rule" astigmatism to which she is not yet adjusted. It is a known fact that people are less tolerant of a full "with the rule" astigmatic correction than of full "against the rule" corrections.

3. The patient may well be one of those persons who have less discomfort when visual acuity is on the blurred side than when it is acute. A fair comparison to this situation may be obtained in considering the fatigue that occurs in looking through opera glasses which improve visual acuity greatly but which may be uncomfortable for prolonged use.

4. Perhaps the most important reason is the fact that this patient has not worn glasses constantly and, for her, a full correction represents a decisive, radical, and probably an extremely different way of using the eyes.

I do not think that the muscle imbalance, in spite of the high normal of 12Δ exophoria for near, is significant in the causation of her symptoms.

MANAGEMENT

The treatment in this case would aim at eventual adequate improvement of vision but the process should be gradual. It is better to undercorrect to a level considerably lower than that tolerated comfortably than to overcorrect above this level of comfort even the slightest degree.

Judgment in this case cannot be perfect, nor are there special criteria for guidance.

I would be guided by the correction the patient had worn in the past, and would order a stronger glass, for example: −1.0D. sph. ◡ −1.75D. cyl. ax. 180°, O.U. This supplies about one half the required cylinder and follows the rule of undercorrection of "with the rule" astigmatism together with undercorrection of sphere so that some ac-

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† Director of Department of Refraction.

commodation at near will be unnecessary. The patient will be told to return in a reasonably short period of time (4 months to 1 year), and at that time gradually increase both sphere and cylinder, until full correction may be accepted, if found desirable.

This woman will soon enter the presbyopic period, so it is likely that she will favor an undercorrection of sphere unless her work requires discriminating distant visual acuity. It is much easier to tell the patient that an undercorrection is purposely being given because a full correction would be too much for the patient's comfort and that, as time passes, fuller correction will be ordered.

243 Charles Street (14).

HEMOSTASIS IN TEAR-SAC OPERATIONS*

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The tear sac and its overlying tissues are supplied with no less than 5 arteries and 4 veins. It follows that any operation associated with the external approach to the tear sac is an aggravatingly bloody procedure and that the task of ligating the vessels is a difficult one.

The most difficult problem, however, is not the large number of arteries and veins in such a small area. It is the lack of mobility of the tissue. This tissue is, for the most part, held very firmly in place by its attachment to the periosteum and the medial palpebral ligament. As a result of this immobility, the edges of the wound cannot be adequately everted and sponged. This makes tying of the seemingly endless number of blood vessels very difficult indeed.

All of this adds up to a bothersome, time-

taking, and, for that matter, a blood-taking procedure which necessitates the use of a suction apparatus. By the time the operation is over, the suction apparatus usually contains almost a pint of blood and probably that much more blood has been swabbed up with sponges.

BLOOD SUPPLY TO TEAR SAC

After several years of contending with this annoying problem, I have devised a remedy which has been completely effective. Before attempting to describe this method, it would be well to consider the blood supply in detail.

The arterial supply to the region of the sac comes from two sources, the ophthalmic and the external carotid. The best known artery is the angular. This artery is actually
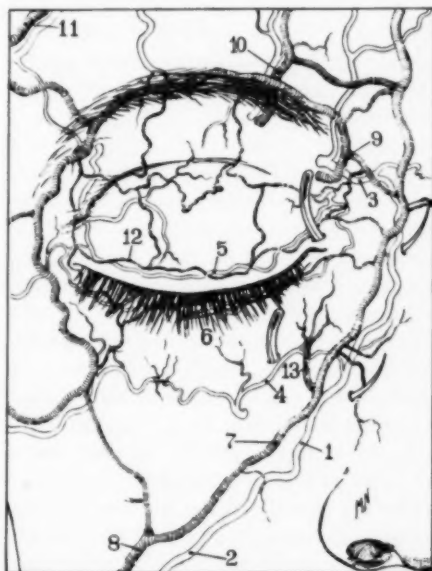
Fig. 1 (Alger). *Blood supply of the tear sac.* (1) Angular artery. (2) Anterior facial artery. (3) Dorsal nasal artery. (4) Infraorbital artery. (5 and 6) Palpebral arteries. (7) Angular vein. (8) Anterior facial vein. (9) Superior ophthalmic vein. (10) Supraorbital vein. (11) Superior temporal vein. (12) Superior palpebral vein. (13) Anastomosis to inferior ophthalmic vein.

a large anastomosis between the dorsal nasal branch of the ophthalmic above and the anterior facial branch of the carotid below. It runs in the angle of the nose and the face, passing about 5 mm. medially to the medial canthus in front of the medial palpebral ligament. It joins the dorsal nasal branch of the ophthalmic artery as it emerges from the orbit about 1.5 cm. above the medial palpebral ligament. There is a lesser blood supply from the infraorbital branch of the internal maxillary branch of the carotid artery and fine branches, called palpebral arteries, come across the lids from the lacrimal and transverse facial arteries.

The veins are somewhat similarly placed. The angular vein runs parallel and just lateral to the angular artery. It joins the anterior facial vein below and the superior ophthalmic and supraorbital veins above. It has a lateral anastomosis by way of the superior palpebral vein to the superior temporal vein. No vein accompanies the infraorbital artery. There is, however, an anastomosis to the inferior ophthalmic vein.

METHOD OF HEMOSTASIS

My method of hemostasis is easily accomplished. It consists of taking two strong sutures, such as No. 2 chromic, and threading one into a needle with a 1-inch diameter, half-circle curve and the other into a needle with a 1.25-inch diameter, half-circle curve. The needles should be of heavy caliber and round. Using a good needle holder, the suture with the smaller needle is placed just above the medial palpebral ligament and a deep bite is taken, commencing at a point 3-mm. above and halfway between the upper punctum lacrimalis and the medial canthus, then extending down close to the lacrimal bone, and emerging at a point on the nose about 1.5 cm. medial to the medial canthus.

Since the second suture should take a broader bite, the needle with the larger curvature is used. The suture should commence at the rim of the orbit where the floor

and the medial wall meet. Staying close to the bone, it should pass across to the nose, emerging on the nose about 1 cm. from the angle.

If the anatomic relation of these sutures is studied, it will be seen that the upper suture blocks off the angular artery and vein before they join the dorsal nasal artery and the ophthalmic vein. The ligature also is below the anastomosis with the superior palpebral artery and vein; therefore, this one suture blocks all blood supply from above.

The lower suture is equally effective. It blocks the lower end of the angular artery and vein, the anastomosis between these vessels, and the infraorbital artery and inferior ophthalmic veins.

The result is a surprisingly effective hemostasis which makes the suction apparatus unnecessary and does away with practically all ligations and sponging. The operator can proceed undisturbed with the operation itself. These ligatures should not be removed until the day following the operation in order to prevent severe bleeding.

SURGICAL TECHNIQUE

The question now presents itself as to how, after placing these two ligations, can the classical incision described in all the texts on ophthalmic surgery be made.

At the American Academy of Ophthalmology meeting in Chicago in 1947, a well edited moving picture by Dr. Michael J. Hogan of San Francisco was presented. His incision for a dacryocystorhinostomy commenced just about at the lower half of the medial palpebral ligament and extended in a straight line downward in the angle of the nose and cheek. I had been making my incision lower than described in the textbooks because of my ligatures but, after seeing his pictures, I commenced to make my incision like his. The results are very gratifying. I now make a lower trephination and get entirely in front and below the middle turbinate. With the incision and trephination in this position, I find that it is no trick at all

to suture both the anterior and posterior lips of the incised sac to the nasal mucous membrane—something I was unable to do when I made the trephination a bit higher up.

Since I could find no mention of this in-

Fig. 2 (Alger). The dotted line shows the technique of incision and trephination formerly employed. The solid line shows the present method of trephination and "Martin-Cordes incision."

cision in the literature, I wrote to Dr. Hogan asking him the history of his method, and whether or not it resulted in less bleeding. He very kindly sent me the following reply:

"The incision has been used by Dr. Robert C. Martin and Dr. Frederick C. Cordes since about 1930. They decided to make the incision lower because they felt that it made the exposure of the sac much easier. They also have told me that, by making it lower, they are able to make it in a straight line. Dr. Martin feels that a straight incision is better than the old curved, or bow-shaped incision, which Mosher and others have recommended. The bow-shaped incision tends to contract and become more curved in time; whereas, a straight incision is parallel with the nose—giving a better cosmetic result. I

do not think they lowered the incision with any idea of avoiding the larger vessels."

It might be well to name this incision the "Martin-Cordes incision" in honor of the inventors.

SUMMARY

A description of the blood vessels in the area of the lacrimal sac is presented.

A method of ligating these blood vessels before making the incision is described. The incision, which I suggest naming the "Martin-Cordes incision," is best suited to this method of ligation.

517 First National Bank Building.

EYELASH BURIED IN CLEAR LENS SUBSTANCE

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Eyelashes as intraocular foreign bodies are not unique. Sharpe[1] reviewed the literature to 1925 and reported 75 cases in the 100 years preceding. Graff[2] reviewed the English literature in 1931 and added 30 cases. Cowen[3] reported 29 cases in 1942. It is, therefore, not by any means a rare complication of ocular injuries. It is unusual, however, when an eyelash is introduced into an eye during an injury in youth, remains to become incorporated into the growing lens and the lens substance surrounding it remains clear. Such a case is here reported.

Review of the literature reveals only one similar case. It was very briefly reported by von Hippel[4] in 1927. It occurred in a 16-year-old patient whose history of eye injury was not available. A cilium was identified in the clear anterior cortex of the lens by use of the slit lamp. Visual acuity in the involved eye was 0.5.

This present case is considered to be unusual enough to warrant rather complete reporting. An abstract of the clinical record and illustrations to show the appearance of the lens follow.

Lieutenant H. L. R., aged 28 years, was referred for eye examination in April, 1948.

History. This patient had no eye difficulty until 1932, when he was 12 years of age. At that time he fell against a window frame containing a projecting nail. This nail punctured his left eye. He was operated within a few hours by an ophthalmologist. About six weeks after the original operation he was again operated; this time for removal of an

The lens of the left eye showed a thin, traumatic, wedge-shaped cataractous opacification at the level of the anterior surface of the infantile nucleus on the temporal side of the lens. It was covered anteriorly by perfectly clear adult nucleus and cortex. Posteriorly, there was a small dense capsular opacity temporally. On the nasal side of the lens was an unmistakable encysted eyelash lying on the posterior surface of the infantile
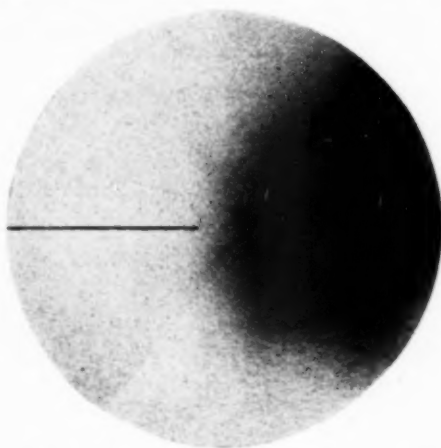
Fig. 1 (Byrnes). Ophthalmoscopic appearance of eyelash buried in clear lens substance. The eyelash can be seen as a thin dark line. Mild traumatic cataractous changes on the opposite side of the lens are due to the original injury 16 years ago.

Fig. 2 (Byrnes). Drawing to illustrate, from above, the location of the eyelash in the lens substance. The locations of the traumatic cataractous changes are also shown.

eyelash from the interior of his eyeball. His eye cleared up and gave him no further trouble. He engaged in athletics and later passed an Air Force examination and learned to fly military aircraft.

Examination. Visual acuity was: O.D., 20/15; O.S., 20/25.

External examination of the left eye showed a small corneal nebula extending from within 1 mm. of the limbus at the 4-o'clock position to within 1.5 mm. of the center of the cornea (result of the old injury).

Cover test revealed a constant convergent, concomitant strabismus of the left eye of about 6 diopters.

nucleus and extending from the equator at the 9-o'clock position almost to the center of the lens. This cilium was entirely surrounded by clear adult nucleus and cortex. It was seen as a thin black line against the red fundus reflex on ophthalmoscopy and was unmistakable under the slitlamp. The eyelash was slightly decolorized and there were gray encysted nodules along its length. Its appearance and location are illustrated in Figures 1 and 2.

This foreign body undoubtedly entered the eye 16 years ago at the time of his accident when he was 12 years of age. The cilium lodged against the posterior surface of his lens where it caused so little irritation that it became encysted and then buried be-

neath the forming adult nucleus and cortex which remained entirely clear. The mild cataractous changes present were on the opposite side of the lens from the cilium and obviously were due to the injury and not to the presence of the cilium.

COMMENT

There is a disagreement as to the reaction of the eye to retained intraocular cilia. Graff[2] states they usually cause no reaction but purulent and plastic inflammation have been reported and he feels it is always advisable to remove them if practicable. Gradle[5] reported a case with a depigmented cilium present for 19 years without reaction. Fox[6] reported two cilia present in a quiet eye for 2 years. McKee[7] reports a case with a cilium present in the anterior chamber for 18 years with no reaction and normal vision. Mattos,[8] Tokuda and Tanaka,[9] and Shagov[10] have all reported similar experiences.

However, Cuvier[11] and von Graefe[12] report sympathetic ophthalmia; Bonnet and Paufique[13] report an iris cyst; and Papogno[14] the formation of posterior synechias following penetration of eyelashes into the anterior chamber. Cowen[3] feels that, like other foreign bodies, a cilium usually produces a severe reaction such as iritis, iridocyclitis, photophobia, lacrimation, synechias, iris cysts, epidermoid tumors, giant-cell development, subsequent cataract, glaucoma, or terminal blindness and often loss of the eye.

Sharpe's[1] case retained the cilia asymptomatically for 33 years at which time the eye became red, irritated, painful, and lost its sight. It was his feeling that apparent early quiescence did not prevent late serious complications of these retained foreign bodies. It would appear, therefore, that removal of cilia is indicated if they are located where such removal can be done without probable damage to the eye. If they are not located where they can be readily removed the risk of leaving the cilia must be balanced against the danger inherent in their surgical removal and decision made on that basis.

In the present case it is believed that the decision made at his operation in 1932, to leave the cilium, was the correct one. Its removal would have jeopardized the patient's sight which at present is excellent. It is unlikely that the foreign body now completely buried in clear lens substance will ever cause any inflammatory reaction in the eye. Whether or not the lens will become cataractous late in life will be a matter of interest.

SUMMARY

A case has been reported in which an eyelash was left in an eye following a perforating eye injury in 1932 when the patient was 12 years of age. This cilium has subsequently become encapsulated and completely buried in the clear lens substance of the adult nucleus and cortex.

Only one similar case has been previously reported in the literature.

School of Aviation Medicine.

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MONOCULAR APHAKIA AND EXOTROPIA CORRECTED BY CONTACT LENSES*

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The correction of monocular aphakia by the use of contact lenses is neither a new nor an infrequent procedure. The correction of monocular aphakia with spectacle lenses has two serious disadvantages:

1. There is a difference of about 25 percent in the size of the images of the two eyes with resulting difficulty in fusion and diplopia.

2. The strong convex lenses before the aphakic eye and a plano or weak spherical lens before the phakic eye introduce prismatic effects which, together with the difference in the size of the images, produce diplopia that makes the wearing of the spectacle lenses difficult and in some cases impossible.

It has also been observed that, when one eye becomes amblyopic but the vision in the opposite eye remains good, the amblyopic eye will tend to diverge. This is especially true if the loss in the visual acuity occurs past the age of 12 years.

CASE REPORT

We are presenting a case of monocular

aphakia and exotropia which was corrected by the use of contact lenses.

History. Mrs. R. C., a white woman, aged 25 years, first presented herself in the clinic of Dr. J. S. Shipman on October 15, 1946, at which time she complained of the inability to see with the right eye. She first wore glasses at the age of eight years. With glasses, her vision in both eyes was always good until she was struck in the right eye in 1936. Since then, her vision in the right eye had become progressively worse. In 1944, she first became aware that her right eye turned out.

Eye examination. Visual acuity was: O.D., hand movements; not correctible; O.S., 6/60, with correction, 6/9.

External examination revealed no abnormalities of the conjunctiva, cornea, anterior segment, or adnexia of either eye. The right eye diverged 15 degrees as measured by the Hirshberg method.

Ophthalmoscopic examination. The right eye was obscured by a posterior lens opacity. The fundus of the left eye was within normal limits. Slitlamp examination disclosed a typical traumatic cataract of the right eye. Diagnosis was traumatic cataract and monocular exotropia of the right eye.

Operations. On December 20, 1946, a discission was performed with a Ziegler knife needle, and on January 17, 1947, a linear extraction performed. Following this, the pupillary space was filled with a dense capsule. On October 15, 1947, a capsulotomy was performed and a good central opening was obtained.

On November 3, 1947, refraction was: O.D., +11.0D. sph., 6/9; O.S., −3.0D.

sph., 6/9. At this time the patient was advised to consider contact lenses for both eyes since the myopia of the left eye required her to wear lenses at all times. Moulds were taken of both eyes after the method of Obrig on December 3, 1947. With the finished contact lenses, her vision (December 10) was: O.D., 6/9 + 2; O.S., 6/6.

Muscle tests. By screen and parallax tests, there was a right exotropia of 25 prism diopters and a right hyperphoria of 5 prism diopters. With the contact lenses, the patient complained of diplopia for both distance and near. Nevertheless, she was urged to wear her contact lenses an hour at a time, increasing this amount each day.

It was contemplated at this time that if the diplopia persisted, we would grind vertical prisms in the contact lenses and overcome the divergence by the use of horizontal prisms in a pair of spectacles.

By January 8, 1948, the patient was quite comfortable and could wear her contact lenses from 4½ to 6 hours daily. There was no double vision for distance or for near.

Screen and parallax tests disclosed 5 diopters of exophoria at both 6 meters and 33 cm. With the Maddox rod, there was 4.5 diopters of exophoria present. There was vertical orthophoria as tested by both methods.

The patient stated that her double vision disappeared within the first week of wearing the contact lenses.

On April 13, 1948, the patient could wear her contact lenses for as much as 8 consecutive hours with no discomfort. The muscle tests on this date were essentially the same as at the last examination.

Comment. This case demonstrates (1) The desire for single binocular vision is so great that it permits a divergence of 15 degrees to be overcome in spite of the disuse of the eye for 10 years; (2) the advantage of the use of bilateral contact lenses in a case of monocular aphakia when the existing ametropia in the phakic eye requires spectacle lenses.

SUMMARY

A case of monocular aphakia with a 15-degree monocular exotropia in the same eye and with a myopia of −3.0D. sph. in the opposite eye is presented.

Correction by the use of contact lenses overcame the exotropia of 10 years' duration and gave the patient comfortable single binocular vision.

2028 Pine Street.
4036 Wilshire Boulevard (5).

HISTORICAL MINIATURE

Your eyes must continue very good, since you are able to write so small a hand without spectacles. I cannot distinguish a letter even of large print, but am happy in the invention of double spectacles, which, serving for distant objects as well as near ones, make my eyes as useful to me as ever they were. If all the other defects and infirmities of old age could be as easily and cheaply remedied, it would be worthwhile, my friend, to live a good deal longer. But I look upon death to be as necessary to our constitutions as sleep. We shall rise refreshed in the morning. Adieu, and believe me ever,

Your's most affectionately,
B. Franklin

From Benjamin Franklin, Complete Works, 1806.

SOCIETY PROCEEDINGS

Edited by DONALD J. LYLE, M.D.

COLLEGE OF PHYSICIANS OF PHILADELPHIA

SECTION ON OPHTHALMOLOGY

April 22, 1948

DR. PERCE DeLONG, *chairman*

HETEROPLASTIC GRAFTS

DR. O. A. CAPRIOTTI (by invitation) and DR. EDMUND B. SPAETH presented a 15-year-old boy from the service of Dr. Spaeth at Wills Hospital upon whom successful isografts had been performed for ectropion of the four eyelids complicating ichthyosis congenita. He was an only child, and there was no history of abnormalities of the skin in either side of the family. Two weeks after his birth, a red rash appeared over the entire body, and this was soon followed by a generalized scaly condition of the skin. The diagnosis of ichthyosis congenita was established when he was a child, and he was presented by Dr. John Ludy at a dermatologic convention.

Epiphora started at about the age of 8 years, and ectropion of the lids was rather severe by the time he was aged 10 years. About 4 years previously, the patient had been treated for 1½ years for a corneal ulcer of the left eye. Prior to admission, he was treated for 3 months as an outpatient for a corneal ulcer of the left eye, with no benefit.

On general examination, the entire body of the patient was covered with brownish scales. The palms and soles were blackish in color and were deeply fissured. The skin of the fact was taut, and there was severe ectropion of both lower lids with a slight ectropion of both upper lids.

Considerable photophobia and marked epiphora were present. The slitlamp showed the right cornea to be clear while the cornea

of the left eye showed some scarring, just below the pupillary area, and an active ulcerative keratitis on the temporal side.

It was obvious that to correct the ectropion, which was the basic cause of the exposure keratitis, a skin graft would be necessary. Since the skin of the whole body was not normal and no members of the family were available, a skin donor was obtained. Patient and donor were of the same blood type and cross matched as to blood type and M, N, and Rh factors.

On January 18, 1948, under Avertin anesthesia, a median tarsorrhaphy was performed on the patient's left eyelids. A linear incision was made parallel to the lid margin, and the skin was freed on either side. A free graft, taken from the donor's thigh, was fitted into the area which had been prepared with thromboplastin solution. The lids were then covered with oiled silk, and a firm pressure bandage was applied. At the first dressing, 10 days later, the isograft was found to be adherent, pink, and free of discharge.

About 20 days later, a similar operation was performed on the right eyelids using the same donor. Ten days later, on first dressing, the graft was found to be adherent, pink, and healthy.

The presence of ectropion in ichthyosis congenita is not a constant feature. According to the cases reviewed from the literature the presence or absence of ectropion depends on the following factors: (1) Whether there is involvement of the face; (2) whether atrophy of the skin occurs; (3) the degree and severity of the skin atrophy.

The skin of the face atrophies, and the skin of the eyelids retracts, thus everting the lid margins. Ectropion of the four lids is extremely rare, occurring only in severe cases and these patients usually die in the first year.

Cases similar to the one presented, and with successful isograft, were reported by Elschnig, in 1912, in the German literature and Shimkin, in 1945, in the *British Journal of Ophthalmology*. In a review of the American literature no previously reported case of this type could be found.

Discussion. Dr. James S. Shipman: This case brings to my mind a case that I saw about 10 years ago which should have had this operation done, and did not. Indeed, it would have been very fortunate for the patient if she could have had this surgery done earlier in life. The patient was a white woman, aged 40 years, who made her living as the "alligator woman" in a carnival. She certainly presented a very marked case of ichthyosis, and there was no mistake about her skin looking like that of an alligator. She had been making a living out of this for many years.

When I saw her, she had hypopyon keratitis with about half of the anterior chamber filled with hypopyon. We did a Saemisch section through the lower third of the cornea and postoperative recovery was fairly satisfactory for about a week. At the end of this time, the patient left the hospital and moved away with the carnival. We saved the eye, but with very little vision. She went down to Richmond and, at my suggestion, reported to Dr. Courtney for a follow-up, but she did not stay with him long. She kept moving on. I cannot help but think that, if she had had such an operation, it would have prevented this serious complication.

I think Dr. Spaeth is to be complimented on this very excellent result. I had the pleasure of seeing this boy at Wills Hospital before and after his operation, and I feel that the result in this case is all that one could ask for. However, if I might be so bold, I would like to suggest to Dr. Spaeth that I would not destroy the beautiful adhesions holding these lids together for at least another six months. The boy is able to see to get around, and I would be too much concerned about these lids turning out again if

they are cut too soon. I do not like to disagree with Dr. Spaeth who has had much more experience with these cases than I have, but I do feel that one must wait a long time before cutting these adhesions.

INTRAOCULAR NONMAGNETIC FOREIGN BODIES

DR. JAMES S. SHIPMAN presented six cases of intraocular copper and described a technique which he uses for the removal of nonmagnetic foreign bodies from the vitreous and the anterior chamber. The first four cases, all with copper in the vitreous, were operated by means of a posterior sclerotomy, through the lips of which a small capsule forceps was inserted. While looking with the ophthalmoscope through the dilated pupil, the operator was able to grasp the foreign body in the vitreous and extract it through the sclerotomy opening. In the first case, the scleral opening was closed with interrupted black silk sutures and no cauterization. In the other three cases, the same method was employed, but the sclera was coagulated around the incision with diathermy before suturing.

The first case made an uneventful recovery, and the vision was normal for 5 weeks following the operation. At the end of this time, a retinal detachment was observed. This became more marked and, approximately 2 months after the original accident, the first retinal detachment operation was done with the Weve needles. This was unsuccessful, and two more retinal detachment operations were performed, Safar pins being employed with the last. These were also unsuccessful. Today, more than 15 years following the patient's injury, the injured eye has no light perception, has a complicated cataract, and is divergent.

The patient in the second case made an uneventful recovery and, in spite of the fact that he has a partial posterior cortical cataract, he has had useful vision, 6/15 with correction, from the time he was first seen until now, almost 15 years after the injury. There was no evidence of any retinal detachment at

any time, and the visual field has remained full.

The third case showed more reaction following operation than the first two cases. The partial cataract which was present before operation became complete shortly after this, and a linear extraction was necessary. Following the cataract extraction, the patient made an uneventful recovery and has had no trouble since. Today, 13 years after the injury, the eye is entirely quiet with normal tension. The vitreous is clear, and the fundus is healthy with no evidence of detachment. The visual field is full, and the visual acuity of the injured left eye is 6/9+ with a +13D. sph.

The fourth case offered a poor prognosis because of the very large foreign body and the massive preretinal hemorrhage which were present when the patient was first seen. A considerable amount of vitreous was lost, and more hemorrhage occurred at the time of the extraction of the foreign body. This hemorrhage persisted, and eventually the eyeball became phthisical. Enucleation of this eye was advised.

The fifth case showed the copper wire to be present in the anterior chamber. This was removed by means of a paracentesis made with a keratome and enlarged with scissors. The foreign body was then grasped with iris forceps and withdrawn. However, the iris became entangled, and had to be replaced through the wound. This resulted in some incarceration but no prolapse of the iris in the paracentesis wound. The pupil was pear-shaped and drawn to the nasal side. A localized opacity still remains on the nasal side of the lens capsule. Otherwise, the media are clear, the fundus is healthy, and both eyes are entirely quiet. The visual acuity without correction today is 6/5, in the right eye, and 6/6, in the left.

The sixth, and last, case reported was one in which the nonmagnetic foreign body was localized in the vitreous. The same procedure, as in the other cases of nonmagnetic foreign bodies in the vitreous, was followed.

However, in this case, we were much more fortunate than in the others due to the fact that after the sclerotomy opening had been made, a bead of vitreous presented with the piece of copper glistening in the center of the bead. This was then extracted with forceps and the necessity for going any deeper into the vitreous was avoided. The scleral wound and conjunctiva were then closed in the same manner as in the other cases. This patient at the present time is still hospitalized, and the outcome is uncertain.

It is now realized that, in the first case, the eye should have been saved. The retinal tear made by the posterior sclerotomy should hav been sealed off, and the detachment could have been cured. Failure to do this was the result of lack of sufficient knowledge about the method for closing retinal tears 16 years ago. In Cases 2, 3, and 5, the results were as satisfactory as one could expect with such drastic surgery. Case 4 was considered very unfavorable when first seen because of the large size of the foreign body and the massive preretinal hemorrhage. However, a larger sclerotomy might have been done earlier. It is realized in retrospect that an an iridectomy should have been done in the fifth case.

I feel that the results obtained in the five reported cases of copper in the vitreous justify the technique followed. However, a special type of forceps, such as a modification of the alligator forceps used by otologists, or a smaller and stronger forceps similar to Thorpe's, might aid in grasping and holding the foreign body. I recognize the fact that if the lens is too opaque for one to see the foreign body, the procedure described cannot be employed. However, since removal of the cataractous lens would be indicated anyway, this could be done first, and then the technique described could be followed through.

Discussion. Dr. George H. Cross: I think that Dr. Shipman has been fortunate in having cases in which the intraocular foreign body could be seen with the ophthalmoscope.

Usually the lens is cataractous or the vitreous is filled with blood or exudate through which it is impossible to see the foreign body. In such a case the foreign body is best removed with the aid of a biplane fluoroscope. By this method the foreign body is accurately located by X rays.

Dr. Shipman was fortunate in that most of the foreign bodies were small ones. He spoke about the use of the endoscope which, to my mind, requires such a large opening in the eyeball.

My experience with nonmagnetic foreign bodies is limited to about 100 cases, 50 of which were operated upon. In many cases the localization was very poor, or the foreign body was outside of the eyeball. In one case it was located in the lower conjunctival cul-de-sac. It is very essential to have a good localization of the foreign body.

If you have a good X-ray report, and cannot see the foreign body and know that it is nonmagnetic, you can try the biplane fluoroscope. I think Dr. Shipman is to be congratulated on the nice results obtained in these cases.

Dr. Edmund B. Spaeth: Dr. Cross has done a tremendous amount of work with the biplane fluoroscope. I know so little about the use of this instrument that it perhaps seems unseemly to discuss its use. In spite of that, I am not at all satisfied or convinced that the biplane fluoroscope is good for the removal of nonmagnetic foreign bodies. The traumatism done to the eye because of the mechanical difficulties connected with the use of the forceps without visualization of the operative field is too extensive for approval.

I do want to speak in greater detail about the use of the endoscope. I have had a fair amount of experience with this, and have found it to be a valuable instrument in cases in which it can be used. Naturally, one cannot use the endoscope when the vitreous is full of hemorrhage.

There are many factors connected with the removal of nonmagnetic metallic foreign bodies from the eye, and many different means of localization and extraction. Each individual case may need an individualized technique. At the best, these cases are frequently difficult problems, and should be studied in detail as to the method most applicable for the situations present.

Dr. Shipman is to be congratulated on his results in these cases. The real tragedies in ophthalmology are those cases in which the foreign body cannot or could not be removed. I believe that, with the exception of zinc and aluminum, every eye with a retained intraocular foreign body will be lost ultimately. In some instances the initial injury, as with lead shot, is so great that the eyes are destroyed irrevocably at the start.

Dr. James S. Shipman: In answer to the remark that it was my good fortune that these foreign bodies could be seen, I do not feel that an opaque lens is a contraindication to this procedure. The lens has to be removed anyway, and, when it is, you can see the foreign body and remove it with the technique as described.

I feel that, in order to see and remove a piece of copper by means of the biplane fluoroscope, the foreign body would have to be quite large. In such a case the eye would be practically destroyed.

I doubt if any of the foreign bodies in the cases we have described could have been seen well enough with the fluoroscope to warrant their removal by that method, since they were all unusually small pieces of copper.

I wish to thank Dr. Cross and Dr. Spaeth for their discussion, and I trust that the report of these cases and the method which we used will stimulate others to try to remove all pieces of copper from the interior of the eye, which can be seen ophthalmoscopically.

CEREBROVASCULAR RESISTANCE AND GRADE OF HYPERTENSIVE RETINAL FINDINGS

DR. IRVING H. LEOPOLD, DR. SEYMOUR S. KETY (by invitation), DR. WILLIAM A. JEFFERS, DR. JOSEPH H. HAFKENSCHIEL

(by invitation), and DR. HENRY A. SHENKIN discussed 21 hypertensive and 3 nonhypertensive individuals who were studied in an effort to find whether or not there was any correlation between the retinal vascular changes and the cerebrovascular resistance in hypertensive individuals. The cerebral blood flows were determined by the method of Kety and Schmidt, and the retinal vascular changes were evaluated according to the classification of Wagener and his coworkers. (See the AMERICAN JOURNAL OF OPHTHALMOLOGY, volume 32, page 365 (March) 1949.)

It was found that a statistically significant correlation existed between retinal changes and the cerebrovascular resistance. The relationship was a direct one in that, as cerebrovascular resistance increased, the grade of retinopathy also tended to increase.

It is evident that the retinal findings do reflect with some accuracy the state of the cerebral circulation, but the degree of accuracy is not marked in that one cannot predict from the ophthalmoscopic findings the exact extent to which the cerebrovascular resistance has been elevated.

Discussion. Dr. Seymour S. Kety: A few words about the physiologic significance of these studies may not be amiss.

As you know, when the physiologist studies hypertension in man, he is impressed with the fact that practically everything he investigates turns out to be normal. Measurements have been made of the output of the heart, and that is perfectly normal. The blood flow through the kidney is essentially normal except in the very late stages of hypertension. The blood flow through the skin, through the periphery of the body, through muscles, and so forth, has always been found to be physiologic. If one calculates the resistance in the blood vessels of these various organs, one finds that uniformly there is an increase in the peripheral resistance through the body, and in any individual organ. Since the brain has been implicated in numerous theories for the etiology of hypertension, we thought it of great interest to study the cerebral blood flow, and finally a method was developed at the University of Pennsylvania which permitted such a determination. We were interested in finding that, in the hypertensive individual, the blood flow in still another organ is perfectly normal. Just the same amount of blood passes through the hypertensive brain as passes through the brain of a normotensive individual.

The interesting thing, however, was that this occurred in the face of blood pressure which might sometimes be twice the normal level. This must indicate a high degree of resistance in the blood vessels of the brain which keeps back the flow of blood that would otherwise be much above the normal.

Dr. Leopold has discussed the possibility that was presented to him as an ophthalmologist; namely, with a method for calculating the resistance in the brain, one could evaluate the clinical impression of clinicians and ophthalmologists that eyeground changes were a reflection of what was going on in the brain. We were gratified to find that there was a fairly good correlation between the two. It is not at all surprising that the correlation is not better because one must remember that we were measuring the vascular resistance at one time (at the time of observation) and that that resistance was a function of the degree of spasticity of the vessels at that particular moment.

The eyeground changes, according to the classification used, are not only a measure of the degree of spasm in the vessels at that particular moment, but also reflect how long that spasm has been going on, and how severe it is. The eyeground changes are not only those of spasm, but also the changes which may result from spasm over a long period of time. If it were possible to separate the various factors that make up a retinopathy, particularly the degree of hypertonus at the time of observation and the results of the past history of that tonus, one might get an even better correlation than

the quite satisfactory one which Dr. Leopold found.

Dr. Francis Heed Adler: I would like to ask Dr. Leopold whether there is any difference in the cerebrovascular resistance in patients with atherosclerosis as compared with arteriolarsclerosis. Dr. Leopold is evaluating the eyeground changes which are admittedly more severe in cases of arteriolarsclerosis. It is possible that cases with atherosclerosis might have high cerebrovascular resistance, and yet would show no pathologic changes in the fundus. Such cases would upset the true correlation between cerebrovascular resistance and hypertensive retinopathy seen in cases of benign and malignant hypertension.

There are still a great many things we do not know about the retinal circulation. We have always taught that the ocular vessels are end arteries, because we say they are like the cerebral arteries. Until fairly recently, we believed that the cerebral arteries were end arteries in the sense of Cohnheim. Lorente deNo states that the cerebral arteries are in no sense end arteries, and that blood cells in the capillaries can pass freely from one end of the cerebral cortex to the other. It may be time that we reinvestigated the retinal circulation to determine more exactly whether there are anastomoses between the various branches of the retinal arterial tree.

Dr. I. S. Tassman: It is difficult to hear a presentation of this kind and be able to digest it and interpret it properly in such a short period of time. It occurred to me to ask a question, especially with reference to the point that Dr. Adler introduced, "Is it possible to correlate the findings of this kind for practical purposes?" The vascular bed in the two organs are of a different nature. There are differences in these structures, as well as possible differences in the arterioles of the brain and those of the retina.

The origin, course, and number of cerebral vessels with their ramifications are quite different from those of the retinal vessels, so that a difference in the vascular

resistance of the two sets of vessels might be expected for this reason. Is it therefore possible to correlate satisfactorily the resistance of the one with the pathologic changes in the other?

Dr. Irving H. Leopold: The normal cerebral blood flows are based mostly on values found in young individuals between 20 and 30 years of age. The hypertensive patients studied here were also in a young age group, approximately 20 to 45 years for the most part. In this group, senile atherosclerosis would probably have a low incidence. The same cannot be said for local atherosclerosis. To date no study has been made to correlate atherosclerotic retinal change with cerebrovascular resistance.

The retinal and cerebral vessels certainly differ in many ways. There is, for example, no cerebral counterpart of the retinal-vessel crossing phenomenon. Nevertheless, there has been evidence presented in the past suggesting that both systems of vessels show similar changes, and this study also demonstrates a significant relationship in the presence of hypertension.

M. Luther Kauffman,
Clerk.

LOS ANGELES OPHTHALMOLOGICAL SOCIETY

May 6, 1948

Dr. Orwyn H. Ellis, *chairman*

Exophthalmos and its surgical treatment

Dr. Howard Naffziger of San Francisco (by invitation) discussed bilateral exophthalmos related to thyroid disease. Since the etiology is not well understood, the literature reflects a wide divergence of opinion. An enormous amount of laboratory work has resulted. Recent investigations have revealed that sympathetic stimulation in man does not produce protrusion of the eye, nor

does paralysis produce measurable retraction, in spite of appearances to the contrary. Late contributions to the literature have avoided this pitfall in interpretation. Statistics show a wide range of variation of the position of the globe with reference to the orbital margin. In thyroid disease a slight exophthalmos is usually present, and following thyroidectomy there is a slight further increase in 40 percent of cases.

In pathologic studies, lymphorrhages were found not only in intrinsic eye muscles, but in the heart, deltoid, rectus, and biceps muscles. The eye muscles were the ones most severely affected. In the orbital tissues there was quantitatively an increase in orbital bulk, relatively greatest in the eye muscles, of which the fat content was doubled. The changes were most marked in the levator superioris, which is responsible for lid retraction. Similar changes have been produced in laboratory animals. Certain chemicals are known to have a marked affinity for orbital tissues, and may produce orbital edema and proptosis.

Clinically the thyroid bears a common but variable relationship to progressive exophthalmos and eye-muscle dysfunction. The thyrotropic fraction of the anterior pituitary body in producing experimental exophthalmos is well known. Thus patients can be divided into two groups, the thyrotoxic and the thyrotropic, the latter being the ones in whom eye signs predominate and evidences of toxicity are relatively insignificant or absent. The degree of exophthalmos and the disturbances of eye-muscle movements do not necessarily run parallel.

Proptosis usually begins months after an otherwise satisfactory thyroidectomy. The extreme cases progress to intracranial infection and death. In its development are seen increasing protrusion, lacrimation, burning, injected and irritated conjunctiva, puffy lids, and limited eye movements. Scleral irritation is a prominent feature. Of the eye movements, the upward movements are the most frequent and the earliest to be restricted, next the lateral movements and least often the downward excursions. Frequently poor vision will be present without evident change in ophthalmoscopic or other findings. Retrobulbar resistance is palpably increased. In the final stages, lack of lid protection because of incomplete closure, protrusion, and edematous conjunctocorneal ulceration are present.

Dr. Naffziger uses orbital decompression to treat these cases. The results of the operation depend greatly on whether or not the muscles show a minimal or marked fibrosis to hyaline change. The surgical treatment consists of enlarging the orbital space to accommodate the increased orbital contents. If the muscles are enlarged with relatively little fluid content, then the recession is immediate. On the other hand if the predominating feature is edema, then the same factors may persist after the operation and additional fluid is taken up until the preoperative balance is reached. These edematous muscles show little infiltration or degenerative change. The use of thyroid with or without iodine in some cases may promote water excretion and thereby lessen the edema. Occasionally unilateral decompressions have been performed due to the predominance of the protrusion on one side. Other methods of surgical treatment have proven of little or no value. Orbital decompression, although carrying little risk, is a procedure of such magnitude that it must be reserved for cases of considerable gravity. Efforts at reducing pituitary function by X-ray therapy have produced no more convincing results than have other general or local forms of therapy.

Daniel B. Esterly,
Recorder.

AMERICAN JOURNAL OF OPHTHALMOLOGY

Published Monthly by the Ophthalmic Publishing Company

SUPPLEMENTS

Accompanying this number of the JOURNAL is a beautiful supplement that is presented to every subscriber. It is officially the *Proceedings* of the Association for Research in Ophthalmology for 1948, and is dedicated to Jonas S. Friedenwald, the first winner of the Proctor Medal for ophthalmic research. It should be highly valued and, in time, will become no doubt a collector's item.

In the past years the *Proceedings* of the Association for Research were collected reprints of the papers read before the association and printed in the JOURNAL a few at a

time. Thus, a copy of the *Proceedings* was not available until all the papers had been published. The method employed was simple and relatively cheap so that the expense to the association was trivial. In return for this privilege, the association granted the exclusive right to the JOURNAL to publish the papers read before that society.

In the past, when there was but a single meeting of the association and only 10 or, at most, 12 papers were presented before it, the agreement was most satisfactory to both parties.

Now, however, with the growth of oph-

thalmic research in this country and the many excellent contributions waiting to be read before the association, it was found necessary, beginning last year, for it to hold its meetings for two days. This healthy and important growth of the association is most valuable to ophthalmology, and is highly significant of our maturity.

The great increase in the number of contributions has created a problem for the JOURNAL and for the association. The problem is solved for the time being by bringing out this Supplement. However, this is very expensive business, especially in these days of inflated costs of printing, and some solution on a more permanent basis must be had for the future.

The trustees of the association are working on the problem which is, of course, a matter of finance, and it is sincerely hoped that the policy of printing the *Proceedings* as a supplement to the JOURNAL will continue, for in this way all the subscribers to the JOURNAL, and this includes most if not all the members of the association, will be assured a copy of the *Proceedings* and the authors a worldwide audience.

The JOURNAL has always been proud of its practical nature. Emphasis has been placed, as an editorial policy, on clinical papers that will be of assistance to those who are on the firing line. Ophthalmic research, however, is playing an increasingly significant role, and papers of this nature should not be buried somewhere and inaccessible to the clinician, for often he can seize upon an idea from the laboratory and apply it with benefit in the clinic.

Thus, a well-balanced ophthalmic journal must have all kinds of contributions if it is to fulfill its important function of bringing new and useful facts to its subscribers. If it is top-heavy on one side or the other, it will alienate groups of readers with loss to all parties.

For this reason the JOURNAL is planning to have a quarterly section, under the editorship of Phillips Thygeson, devoted to some phases of ophthalmic research in the form of preliminary reports and other items of interest. It is also the policy to publish, as usual, papers of research nature as they come over the editor's desk that, in his opinion, warrant publication.

The JOURNAL is happy to present this historic Supplement. It represents a great deal of work and effort on the part of officers of the association and a pleasurable task for the JOURNAL.   Derrick Vail.

NIGHT DRIVING

Motor vehicle fatalities have increased steadily with the travel mileage, the present toll being over 32,000 deaths annually. Night accidents are twice as likely to be fatal as those of the day, the deaths per accident being respectively 1 to 26 and 1 to 49. The fatal accident rate per mile at night is three times that of the day. Although only one third of the driving is done at night, two thirds of the traffic deaths then occur. Motor vehicles cause more loss of life among other road users than among their own occupants. Of the pedestrians, 70 percent were killed at night.

The three most important visual factors involved in night driving are: (1) discrimination under conditions of poor illumination, (2) ability to see against glare, (3) recovery from glare. Tests designed to test these faculties should be simplified and adapted for the driver's examination. Glare resistance measures the ability to distinguish a dimly illuminated object when bright lights are shining in the eyes at various angles. To test glare recovery the adapted eyes are first checked for discernment of a dimly illuminated object, then exposed to a glaring light for 30 seconds, after which the interval is noted before the dimly illuminated object can again be perceived.

Signals composed of reflector buttons, five-eighths inch in diameter, are visible at 1,000 feet. The return beam from the headlight does not exceed 0.000,001 foot-candles

at this distance. At a driver's eye level the high beam of an oncoming car gives 1.0 foot-candle. The pupils contract within one second, but require seven seconds to fully redilate, and adequate readaptation takes one minute. The effect of glare in reducing peripheral vision depends on how greatly the glare light contrasts in intensity with the general illumination and its angle of incidence. The effect at one degree from the line of vision is over three times that produced at five degrees. Hence shifting the gaze down to the right edge of the road materially reduces the glare effect. Likewise, when the opposing headlight beam is depressed, the light seen is reduced from 1 foot-candle to 0.2 foot-candle, and the glare effect is proportionately less.

The prime reason for the excess of night accidents is inadequate vision. A shorter sight distance results and, because of unreliable visual clues, errors in the judgment of distance and speed occur. As the illumination lessens, the field of vision decreases, especially so when fatigue develops. About 75 percent of accidents have involved objects in the peripheral field.

As a visual deficiency in daylight is even more significant at night, the one-eyed person and those with corrected acuity below 20/40 should be cautioned especially against night driving. Motorists with only one efficient eye, which includes 1 to 2 percent of all drivers, are much inferior to the binocular sighted in night vision, glare resistance, and recovery from glare. A similar deterioration, though without loss of acuity, often affects the aged due to the rigid iris not dilating adequately or to the media being less transparent to the rays most sensitive to the dark-adapted retina. Fatigue from night driving prolongs the glare recovery time, and the accident-prone drivers often show a significant deficiency in dark adaptation.

The hazards of night driving can be reduced by improved highway lighting. This has been feasible only in congested areas, but two thirds of all accidents happen in the country. Accidents have occurred at speeds below 20 miles per hour so that it seems hardly possible to get the speed of vehicles down to a safety level. Polarized light to reduce glare is impracticable as the headlights would then require over four times the present power and dust on the screens would modify the filtering effect.

But various simple measures are worth while. Light objects are discerned with only one fourth as much light as dark objects. When a light road surface in the environs of Philadelphia was changed to dark a marked increase in night accidents followed. Pedestrians should not only face the traffic in walking but at night should wear something white if only a handkerchief around the neck or arm.

Spectacles, although necessary, cause a loss in light transmission. Tint aggravates the absorptive light loss and so any kind of tinted glass should be taboo after nightfall. In clear crown glass of 1.5-mm. center thickness only 0.6 percent of light is absorbed. However, the loss from surface reflections is significant—4 percent from each surface in crown glass, 6 percent in flint glass. Moreover the reflections cause secondary images with consequent haze and reduction of image quality. The magnesium fluoride coating cancels almost completely the reflected light in flint glasses and lessens considerably the loss in crown glasses. On changing to thinlite coated lenses, the appearance of myopes is remarkably enhanced and a subjective improvement in vision is experienced, especially at night.

Glasses have been constructed that effectively lessen the disturbance from headlight glare. For the past year the Night Driving Lens Company of New Haven, Connecticut, have been making up the driver's distance prescription in a clear glass on which has been placed a small mirror shield just to the left of the pupillary margin in each eye. The shield is a thin front-surface mirror that permits clear vision through it. It is probably made of inconnel (an alloy of chrome, iron,

and nickel) and is guaranteed to be harder and more resistant to wear than the glass itself. The mirror reflects the headlight glare and, at the same time, casts a protecting shadow across the pupil. Dr. W. J. Holmes of Honolulu, who has been much concerned about the problems of night vision, and I have given these glasses a trial for the past six months and can confirm their value. The coated lens mitigates a different disturbance of night vision from the "silvo-flect" shield, but the two cannot be combined, as the magnesium fluoride coating cannot be successfully applied to the latter.

In prescribing special glasses for night driving, the oculist should recall that the greatest luminosity of the spectrum shifts from 555 millimicrons (yellow-green) in day vision to 510 millimicrons (green-blue) at night. The focus of the eyes changes accordingly so that the eye is functionally about 0.5D. more myopic in night vision. Consequently, to obtain the clearest vision at night a $-0.5D$. should be added algebraically to the regular distance prescription to compensate for the night myopia.

James E. Lebensohn.

THE AMERICAN BOARD OF OPHTHALMOLOGY EXAMINATIONS

If the results of the American Board of Ophthalmology examinations can be taken as an index of the general level of ophthalmic education throughout the country, the prospect is pleasing. Some years ago 25 to 30 percent of the candidates taking the written test failed and were not admitted to the practical. At the recent written examination held in January, 1949, only 11 percent failed.

This definite improvement may be interpreted in several ways—the questions asked are easier, the examiners are becoming more liberal in their grading, or the candidates are better prepared. A study of the situation reveals the last interpretation to be the most likely. We are now seeing the first crop of postwar trained men who have completed three years in ophthalmology. There is no doubt that the laudable efforts made by the universities and by the Ophthalmological Study Council in giving basic courses are bearing fruit.

The fact that many more men are now being prepared to take the examination has contributed greatly to the work of the board. Last January, 256 candidates, a record number, took the two-day written examination in 34 cities throughout the country with the result that it has been necessary to schedule three practical examinations during the remainder of the year. The board appreciates the coöperation of ophthalmologists who have given their services in proctoring the written examinations and who have acted as associate examiners in the practical. Without them it would be impossible to examine such large numbers of candidates.

It is the feeling of the board that the written examination should be held only at medical schools and hospitals and that the local head of the department of ophthalmology should be responsible for conducting the examination, either proctoring it himself or delegating this important function to a member of his visiting staff. Efficient proctoring by an ophthalmologist is essential even though it entails some sacrifice of time and money once a year. Since the board members themselves serve without pay, it is not too much to ask the proctors to do likewise. In this way they can help make their contribution to ophthalmic education.

Edwin B. Dunphy.

OBITUARIES
JOHN GREEN
(1873-1949)

To understand John Green, a knowledge of his background is necessary. If all of the readers of his obituary were of the older generation, no description of his father

JOHN GREEN

would be necessary, but for the younger ones something must be written.

John Green, Senior, was one of the most eminent ophthalmologists of America and a dominant and dominating factor in the early history of the specialty. For many years he was chairman of the powerful membership committee of the American Ophthalmological Society and, when it was voted to elect this officer annually, Dr. Green withdrew from activity in the society. He was famous for his originality of thought

and his brilliant mind. Being so constituted, it was natural that he thought that St. Louis schools were not good enough for his son, John Junior, and so had him taught privately until time for him to go to college. This made adjustments hard at Harvard for the boy who had never learned to play with his fellows. He had the further handicap of being very young, only 16 years old, when he matriculated. Hence the young boy, with very limited experience in making acquaintances, probably did not get as much from his university association as others who were more mature.

Of splendid mentality and the son of such a distinguished father, Dr. John Green was certain to become an outstanding figure in ophthalmology. But, because of his heritage and training, there was always about him some shyness and sensitivity, and, well liked as he was by his associates, because of this he was at times somewhat reticent.

He studied to be well informed on everything pertaining to medicine and kept himself young by his eagerness to learn and his active association with ophthalmological societies, national and local.

His written contributions were largely clinical because the practice rather than the theory of medicine intrigued him, as one might expect from a man who was always busy with patients and spent little time in laboratories.

When he returned to St. Louis from Cambridge, in 1894, he studied medicine in Washington University Medical School from which he was graduated in 1898. He was then associated for a brief period with a well-known general surgeon, but soon took up the study of ophthalmology in his father's office. For a number of years he practiced with him, but the two very positive natures struck sparks so often that the younger man opened an office for himself and formed an association with Dr. William F. Hardy which was continued for many years.

In 1902, Dr. Green married Lucretia Hall

Sturgeon and of this union six children were born. They were: Helen C. (Mrs. Leonard Lee Bacon), Harmon, John, Nathaniel Pope, Lucretia H. (Mrs. William C. Lindsley), and Elizabeth. His wife and children all survive him.

Never deeply interested in athletics, Dr. Green did, however, devote some time to tennis and in his early days could often be seen on the courts of the St. Louis Amateur Athletic Association.

He became a member of the staff of the ophthalmological department of Washington University Medical School at the time of its reorganization in 1910. He worked in the clinic there for a few years and then transferred to St. Louis University where he rose rapidly to the rank of professor.

His chief interest outside of his family was his profession. An avid student, he was a regular attendant at the St. Louis Ophthalmic Society meetings to which he contributed many interesting papers and discussions. In the early days, this organization was confined to 12 members and was of a very informal nature where participation in the discussions was general. Dr. Green invariably contributed something of value. An interesting feature was the annual calamity meeting at which each member described his most distressing case of the year. This served the double purpose of getting expert advice, a sort of curbstone consultation, and of raising the morale of each member when he heard of the awful things that happened to others! Unfortunately as new members were added, expediency occasioned the discontinuance of this meeting. There are now 45 members of this society, and it would take a long time to listen to all of the sad tales and there would be no tears left to shed for the last raconteur!

Dr. Green was naturally one of the early presidents of this society. He was always interested in its activities and was one who insisted on maintaining a high ethical standard and good quality for the papers presented. To him and to men like him can

the society turn in appreciation for the excellent quality of the programs delivered at its meetings and the great esteem with which ophthalmologists are held in St. Louis.

Dr. Green was truly civic minded. He was a member of the Board of Education, University City, from 1910 to 1920 and a member of the Board of Health from 1921 to 1926. From 1906 to 1910 he was secretary of the Joint Medical Council, an organization to change the plan of administration and control of public hospitals in St. Louis.

Of his many honors and achievements only three can be here detailed. First, and very dear to his heart, was hi. secretaryship of the American Board of Ophthalmology. He held this office from 1933 to 1943 and, during his final year on the board, was its chairman. The second honor was the chairmanship of the Section of the American Medical Association in 1936, and third, and perhaps most highly prized, was his election to the presidency of the American Ophthalmological Society in 1944.

John Green was a jolly fellow, always ready for a laugh, a fine companion. He loved the Racquet Club, a man's club, where he often foregathered of an evening with his friends. His was a happy life, a long life, full of achievements. He never did live to get old. The remark oftenest to be heard from his colleagues in the days after his death was, "I didn't realize that John was 75." When he died, the world lost a fine doctor and his confreres a loyal friend.

Lawrence T. Post.

LOUIS BOTHMAN
(1893-1949)

Dr. Louis Bothman was born on November 16, 1893, at Saint Louis, Missouri. He died of coronary disease on January 19, 1949, at Chicago. After finishing high school at Murphysboro, Illinois, he entered the University of Chicago from which he received his B.S. degree in 1913. In 1917, he received his M.D. degree at Rush Medical College.

Deciding to specialize in ophthalmology, Dr. Bothman worked for five years on half-time at the University of Illinois College of Medicine. He spent a short period at the Illinois Eye and Ear Infirmary and six months' study in Vienna in 1926. In 1932, he went to India for intensive study of cataract surgery. He also did considerable graduate work in physiology at the University of Chicago.

From 1926 to 1941, Dr. Bothman was first assistant and associate clinical professor of ophthalmology at Billings Hospital, University of Chicago. He was attending ophthalmologist at St. Luke's Hospital, being senior attending ophthalmologist at the time of his death. From 1941, he was clinical professor of ophthalmology at the University of Illinois College of Medicine.

Dr. Bothman had a fine, precise mind, was a careful observer and reporter and an enthusiastic, devoted teacher. In particular he was a close student of ophthalmic literature and was leader of the Eye Journal Club, a group of 40 to 50 men who met monthly

LOUIS BOTHMAN

for 10 or 12 years in an assigned study of the most recent ophthalmic literature. From 1932 to 1949, he edited the eye section of the Eye, Ear, Nose, and Throat Yearbook, a work that has been highly praised by Dr. Arnold Knapp. In addition, Dr. Bothman made many contributions to ophthalmic literature. Many of his papers were concerned with eye surgery in which he was deeply interested and very proficient.

For many years—17, in fact—Louis Both-

man and I were closely associated in the care of patients, in study, writing, and teaching. I found him to be an even-tempered, considerate man, keen and thoughtful, with whom it was a pleasure and satisfaction to work. During all those years, I am proud to say, neither of us ever had a cross word for the other.

Any man who has lived and felt as intensely as did Louis Bothman—and he did feel intensely about many things and persons—and still be as wisely tolerant as he, commands profound respect and admiration. We deeply mourn his passing.

                              E. V. L. Brown.

CORRESPONDENCE

NOTICE OF MEETINGS

Editor,
American Journal of Ophthalmology:

This is simply a note to let you know that I appreciate reading the "News Items" for the scheduled meetings in the JOURNAL. However, I would like to add that there is so little time between the dates of the meetings and the time when the JOURNAL is received, that it is practically impossible to plan to attend one on such short notice.

It would be greatly appreciated if more time, either through a separate "News Items" sheet announcing these dates could be received, or more advanced notice made possible in the JOURNAL.

                    (Signed) Bernard B. Friedman,
                         Corpus Christi, Texas.

EDITOR'S NOTE

The matter of getting advance notices of meetings, graduate courses, and so forth has given the JOURNAL considerable concern. In order to give advance notice of these meetings, it is necessary that information concerning them be received by the JOURNAL three months prior to the meeting.

USE OF AIR TUBE DURING LOCAL ANESTHESIA

Editor,
American Journal of Ophthalmology:

On patients undergoing surgery of the eye it is necessary to cover the face with drapes which frequently cause anxiety to the patient, and this is often manifested by air hunger. Such anxiety may result in restlessness and tenseness, thereby making the operative procedure more difficult and more hazardous.

During the past two years at the Eye Institute, all patients under local anesthesia have had an air tube placed under the drapes in an effort to relieve these unpleasant symptoms. A long rubber tube is attached to the air jet in the operating room and pinned to the drapes near the base of the neck before the sterile part of the drapes has been applied. The air is turned on so that there is a gentle flow coursing up over the face. There is a remarkable quieting effect on the patient when the air is turned on and the patient is visibly relaxed.

Not infrequently, elderly patients may become disoriented shortly after operation. This condition, seen in those who have had preoperative sedation in the form of barbiturates or other sedatives, is thought to be due to a cerebral anoxia in a person with poor circulation who is further embarrassed by the sedation and heavy drapes about the face. Since the air tube has been used, this postoperative disorientation has not been a serious problem. In some patients in whom the circulation is extremely poor and the vital capacity is very low, oxygen has been substituted for the air with very gratifying results.

                    (Signed) Joseph A. C. Wadsworth,
                              New York.

BOOK REVIEWS

AN INTRODUCTION TO CLINICAL ORBITO-
NOMETRY. By A. C. Copper, M.D. Leiden,
Stenfert Kroese, 1948. 117 pages, illustra-
tions, diagrams, and bibliography. Price:
Clothbound, $3.00; paperbound, $2.25.

There has long been a need for a simple
instrument, comparable to the tonometer,
that would give some degree of accurate
estimation of the orbital tension, especially in
those conditions that cause an increase in the
intraorbital pressure. The clinician in the
past has had to be satisfied with the sense
of resistance to digital palpation on pushing
the eye back into the orbit. Dr. Copper re-
views the efforts of scientists to devise an
instrument that would give a reliable index
of orbital tension. He points out that Lang-
enhan was the first to describe such an
apparatus in 1910. Since then, there have
been several attempts to improve on the idea
and to devise new instruments. Gutmann,
in 1914, presented an instrument similar to
the Schiøtz tonometer, by which he applied
increasing amounts of pressure directly on
the cornea. He named his apparatus the
"piezometer." There were many disadvan-
tages to this instrument and the clinical
use of it was disappointing.

Copper has invented an instrument that
may turn out to be of great use to the in-
ternist and to the ophthalmologist. By it one
can apparently measure the variation of the
orbital tension from the normal, and con-
struct curves that yield information as to the
character of the lesion behind the eyeball,
that is to say whether it is of solid or fluid
nature. This should be particularly useful, as
the author points out, in helping to decide
whether the proptosis is of the thyrotoxic or
thyrotropic type, and may be a very impor-
tant factor in determining whether or not
thyroidectomy is indicated.

He also presents some evidence that with
it one can get some help in determining
whether a solid growth is in the temporal

or nasal side of the orbit. Tumors can be
diagnosed even in the absence of proptosis.
It will not reveal the nature of the new
growth, of course. It is only capable of dis-
closing the presence of abnormal density in
the orbit and of deciding whether the process
is stationary or progressive.

Copper's instrument consists of a bridge,
not unlike that of the Hertel exophthalmom-
eter, resting on each outer orbital rim and
the nose. The patient lies down and this
bridge is adjusted and held in place by a
headband. The eyes are directed forward in
the primary position. A plastic contact glass,
on the apex of which is fitted a small cylin-
drical projection, is applied to the cornea.
A dynamometer similar in principle to that
of Bailliart and calibrated to represent pres-
sures up to 400 gm. is passed through a slit
in the bridge, and the plunger of the instru-
ment is lightly inserted into the cup on the
apex of the contact glass. The eye is then
displaced backward into the orbit by steadily
increasing the pressure of the plunger. Vari-
ous readings up to 400 gm. of pressure are
taken and a curve of values is constructed.

The author concludes that (1) Orbitonom-
etry is a valuable diagnostic aid in patho-
logic intraorbital conditions, and (2) orbito-
nometry assists in approaching the patho-
physiology of certain endocrinal diseases,
especially those in which the pituitary and
thyroid glands are concerned.

The book is well and clearly written. It
opens up a field of investigation which is
so important that every ophthalmologist
should be acquainted with the subject.

                                        Derrick Vail.

MANUAL DE OFTALMOLOGÍA CLÍNICA Y
TEÓRICA (Manual of Clinical and Theo-
retical Ophthalmology). By Dr. Manuel
Márquez, ex-professor of ophthalmology
of the University of Madrid, professor
of ophthalmology of the School of Rural
Ophthalmology of the National Polytech-
nic of Mexico. Book 1, General Clinical

Ophthalmology and Defects of Refraction of the Eye. 274 pages, with 311 figures, and 7 plates, of which 6 are in color. Mexico, D. F., 1949. Imprenta "Grafos."

Spain's political upheavals have scattered some of its prominent citizens to other parts of the world. Manuel Márquez is one of these distinguished former citizens, now active in the city of Mexico. The publication of the present volume is credited by the author in part to the desire of his Mexican students for reproduction of his ophthalmological lectures and partly to the fact that the first two editions of his original manual, published in Europe, have been exhausted.

Dr. Márquez's fame as a teacher of ophthalmology is universal throughout the Spanish-speaking world. This new volume is well printed on excellent paper. It contains a good many new illustrations, a number of them by Dr. Márquez's companion in exile, Dr. Rivas Chérif of Mexico City. The volume deals with ocular anatomy, physiology, and pathology; defects of refraction and accommodation, and their diagnosis by subjective and objective methods; diagnosis of fundus diseases and diseases of the anterior segment; and therapy of the eye and of the general system in relation to the eye. Characteristic of the author's high professional standards is the devotion of a special chapter to "Ophthalmologic Deontology," the science of professional duties and etiquette.

W. H. Crisp.

MALATTIE CUTANEE E VENEREE ED ALTERA-ZIONE OCULARI. By G. Sala and P. Noto. With a foreword by Prof. A. Crosti and Prof. B. Alajmo. Palermo, Italy, S. F. Flaccovio, 1948. 410 pages, bibliography. Price, $3.00.

A very important Italian publication is this volume by an ophthalmologist and a dermatologist, showing the close relation of these two branches of medicine. The authors did not limit their observations to the diseases of the skin surrounding the eye, which can be found in any textbook, but made a complete clinical and pathologic study of generalized diseases of the skin affecting the inner eye.

The volume of 410 pages is divided into 16 chapters, which include: Epithelial dystrophies, allergic dermatosis, dermatosis from parasites, from infection, from avitaminosis, precancerous lesions, hemorrhagic syndrome, venereal diseases, and so forth.

A large bibliography completes this interesting and well-written book, for which the authors deserve enormous credit.

Vito La Rocca.

REFRACTION OF THE EYE. By Alfred Cowan, M.D. Philadelphia, Lea & Febiger, 1948. Edition 3, thoroughly revised. 287 pages, 187 illustrations, 3 colored plates, bibliography, index. Price, $5.50.

The appearance of the third edition of this justly popular book is a testament of its value to teacher, student, and practitioner. The author, who is professor of ophthalmology, Graduate School of Medicine, University of Pennsylvania, has devoted his professional career chiefly to the study and the teaching of refraction. The integrity of his work illuminates every page. His common sense in the handling of this assignment is in refreshing contrast to many other books on the same subject.

Those who possess the earlier editions will want this one to bring them up to date. Those who have not seen or owned an edition have an ophthalmic treat ahead of them. It is highly recommended.

Derrick Vail.

TRANSACTIONS OF THE OPHTHALMOLOGICAL SOCIETY OF NEW ZEALAND, Supplement to the New Zealand Medical Journal, 1948.

The transactions begin with the presidential address of Rowland P. Wilson which is a scholarly treatment of various facts of

etiology, pathology, and diagnosis of certain bacterial and allergic diseases of the conjunctiva.

Bruce Hamilton discusses choroidal sarcoma. It is 8 times as common in Tasmania as in England; 11 cases were followed 10 years and, in this small number, the mortality was 27 percent, as against 55 percent in England and 66 percent in the United States. The depth of pigmentation seemed to have a definite relation to the mortality rate. The author presents a family tree of five generations, two members of which, a woman and her niece, died early of choroidal sarcoma.

Fairclough calls attention to cataract in myotonic dystrophy. His report is illustrated with drawings of the lens and photographs of each of six patients. There are shorter discussions of pterygium, herpes, and varicella, retinal detachment, prevention of industrial accidents, penetrating wounds, contact lenses, and dislocation of the lens.

F. H. Haessler.

TRANSACTIONS OF THE OPHTHALMOLOGICAL SOCIETY OF PARIS (and of the Ophthalmological Societies of the East, of Lyon, and of the West). Meeting of April, 1948, pp. 105-245.

Hudelos demonstrated a new instrument, the retinal esthesiometer, and discussed the technique of its use and the importance of this more refined test in the prognosis of cataract extraction, organized pupillary exudate, and detachment of the retina. It is of value in detecting field defects in mentally disoriented patients.

A. M. Larmande described a case of craniofacial dysostosis in which a decompression of the orbit and the optic canal caused a regression of the exophthalmos and improvement of vision. Armand de Gramont demonstrated his new instrument for retinal photography.

Velter reviewed his 40 years of experience with sclerecto-iridectomy in the treatment of glaucoma, and Mercier reported surprising success from the subconjunctival implantation of autoclaved placenta in three cases of intractable iridocyclitis.

Legrand recommended iridectomy and tarsorraphy in severe tuberculosis of the anterior part of the eyeball. It gave him better results than any other specific or nonspecific treatment.

In his lecture on periodic and local variations of certain ocular diseases, Professor Brückner pointed out that pterygium, rare in central Europe, is very frequent in Central and South America and in Africa. Koch-Weeks conjunctivitis, which is very rare in Europe, is common during the summer months in Africa and Asia Minor. He also noted differences in the occurrence of diseases associated with inclusion bodies, gonoblennorrhea, phlyctenular conjunctivitis, tuberculous, herpetic, and syphilitic diseases of the eye, and serpiginous ulcers, as well as nutritional and metabolic disturbances. There is also an extensive analysis of the variations of glaucoma and vascular diseases, many charts and statistics, and a bibliography.

Jean Nordman discussed the congenitally luxated lens as a malformation of the eye only, distinguishing it from those associated systemic congenital anomalies. Thomas and Muller reported a case of orbital Schwannoma without any manifestations of Recklinghausen's disease. Gallois recommended diascleral transillumination for localization of intraocular foreign bodies close to the ciliary region.

Brückner and Jazbasic read a paper on the experimental hypertensive retinopathy in dogs and the possible value of the findings in the surgical treatment of hypertension. Cordier and Pissavin analyzed the occurrence of the Argyll-Robertson sign in herpes zoster ophthalmicus.

Alice R. Deutsch.

ABSTRACT DEPARTMENT

Abstracts are classified under the divisions listed below. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

CLASSIFICATION

1. Anatomy, embryology, and comparative ophthalmology
2. General pathology, bacteriology, immunology
3. Vegetative physiology, biochemistry, pharmacology, toxicology
4. Physiologic optics, refraction, color vision
5. Diagnosis and therapy
6. Ocular motility
7. Conjunctiva, cornea, sclera
8. Uvea, sympathetic disease, aqueous
9. Glaucoma and ocular tension
10. Crystalline lens
11. Retina and vitreous
12. Optic nerve and chiasm
13. Neuro-ophthalmology
14. Eyeball, orbit, sinuses
15. Eyelids, lacrimal apparatus
16. Tumors
17. Injuries
18. Systemic disease and parasites
19. Congenital deformities, heredity
20. Hygiene, sociology, education, and history

11

RETINA AND VITREOUS

Maione, Mario. **Contribution to the pathogenesis of senile macular degenerations.** Ann. di ottal. e clin. ocul. 73:321-331, June, 1947.

Maione presents two cases of disciform degeneration of the macula, one, bilateral, in a 39-year-old woman and the other, unilateral, in a 78-year-old man. Both patients had diffuse arteriosclerosis. In the second patient the unaffected eye showed pigmentary dystrophy in the macular region. It is probable that the pigment epithelium participates in the evolution of the disease and undergoes dystrophy because of circulatory disturbances. (4 figures, references.)

Harry K. Messenger.

Moeschlin-Sandoz, Y. **Senile pseudotumor of the macula with multiple lesions.** Ophthalmologica 116:272-276. Oct.-Nov., 1948.

A case of senile disciform degeneration of the macula was followed for 18 years. Through the patient's death the eyes became available for histological examination. There is no difference in principle between the markedly elevated and the flat forms of disciform degeneration of the macula.   Peter C. Kronfeld.

Neame, H. **Angiomatosis retinae, with report of pathological examination.** Brit. J. Ophth. 32:677-689, Sept., 1948.

Three cases of angiomatosis of the retina are presented in detail. One of the eyes was enucleated and was studied histologically. There are two distinct clinical types of this disease, a pale pink swelling associated with swollen retinal vessels and enclosed in a capsule or sheath; and a blue venous swelling. Unless treated, eyes with tumors of the first type become blind. Radium, radon, X ray, electrolysis and perforating diathermy were used but vitreous hemorrhages, retinal cystic degeneration, retinal separation and cataract may follow. The cause of the detachment without subretinal exudate or tears is not known. (9 figures.)   Morris Kaplan.

Peck, F. B., and Mann, M. **Effect of hesperidin methyl chalcone (vitamin P) on diabetic retinopathy.** Am. J. M. Sc. 217:277-282, March, 1949.

A group of diabetic patients was studied

to determine the effect of vitamin P on diabetic retinopathy. Prothrombin and capillary fragility were measured; the level of plasma proteins was also determined.

The authors present the following conclusions. There was no significant alteration in the plasma albumin or globulin of 23 diabetics, twenty had evidence of diabetic retinal changes. The prothrombin time and retinal changes were greater in patients who had diabetes more than 10 years. The relationship, if any, between prothrombin time and diabetic retinopathy deserves further study. One half of the patients with retinopathy had increased capillary permeability, but this manifestation was not correlated with prothrombin time. In many cases, the petechial index improves with administration of vitamin P, suggesting that this vitamin has some effect on capillaries but the retinal hemorrhages do not change. Retinal hemorrhages are seen in diabetics, who do not show increased capillary fragility. Vitamin P did not alter the course of diabetic retinopathy in a majority of these patients.   Theodore M. Shapira.

Philips, Seymour. **Scleral resection in the treatment of retinal detachment. (A preliminary report.)** Brit. J. Ophth. **32**: 811-818, Nov., 1948.

Causes of failure in the usual diathermy repair of retinal detachment are failure to see and then seal off the tear, retraction of the vitreous and shrinkage of the retina so that it is too small and does not fit the globe. When the retinal tear can be seen, then diathermy remains the procedure of choice; however there are very definite indications for the employment of scleral resection. These are multiple tears in a thin atrophic retina where diathermy has failed, detachment in which no tear can be found, long standing detachment of a shrunken retina that no longer fits the globe, and high myopia. In the latter vitreous retraction and atrophic retina give little hope of success with diathermy.

Scleral resection shortens the globe and allows the shunken vitreous and retina to fit. It may encircle the whole globe or be limited to any part of it. In local anesthesia a slice of sclera about 4 mm. wide is removed with scissors. At the same time interrupted white silk mattress sutures are placed in the area from which tissue is being removed. Postoperative treatment is the same as for diathermy repair. Two successful cases are reported. (5 figures.)   Morris Kaplan.

Philips, Seymour. **Retinal venous changes in diabetes.** Tr. Ophth. Soc. U. Kingdom **66**:231-239, 1946.

Ballantyne, in 1943, described the changes found in the larger retinal veins in diabetes and concluded that the venous anomalies may occur in the absence of hemorrhage and exudate. He had not observed their development from an earlier phase and found that they usually occurred in mild as well as in controlled diabetes. He describes a patient, 51 years of age, whose diabetes had been controlled by insulin for four years and whose vision had become blurred four years before. He ascribed the lesions to phlebosclerosis associated with arteriocapillary fibrosis in the islands of Langerhans. Similar retinal findings in a patient with advanced phlebosclerosis from fibrosis of the lungs and an undoubtedly increased venous pressure suggest that the retinal venous changes may have a mechanical origin. The vitreous pressure may vary through a wide range in those taking insulin. An increase in blood sugar produces a diminished intraocular pressure. Constant changes in vitreous pressure for a long time might lead to phlebosclerosis. (5 figures.)

Beulah Cushman.

Radnót M. **Formation of new blood vessels in diabetic retinitis.** Klin. Monatsbl. f. Augenh. 113:137-140, 1948.

The formation of new blood vessels is an important finding in diabetic retinitis of severe character. Vascular hypertension and damaged kidneys are often found in conjunction with diabetes and diabetic retinitis. The author feels, however, that the formation of new blood vessels is solely due to diabetic changes. It corresponds to the pathological finding of rubeosis iridis, also found in diabetes. The literature concerning retinal hemorrhages in diabetes is briefly reviewed. A clinical case of diabetic retinitis and the histologic findings in another in which there were newly formed retinal vessels, are described. (1 color plate, 2 figures, references.)   Max Hirschfelder.

Saebø, Johan. **Atrophia gyrata choroideae et retinae.** Brit. J. Ophth. 32:824-847, Nov., 1948.

Much confusion in the literature exists concerning the clinical aspects of atrophia gyrata choroideae et retinae and especially as to the possible relationships between this disease and choroideremia. Two divergent conceptions concerning this relationship have persisted; in one the two diseases are the same disease of which choroideremia is the ultimate stage and in the other choroideremia is a defect or malformation whereas atrophia gyrata is an acquired progressive degeneration. To complicate things further, both have often been confused with retinitis pigmentosa; and indeed, the main features of atrophia gyrata are often found in pigmentosa, namely familial occurrence with frequent history of consanguinity, night-blindness, reduction of central vision, defect of the visual field and an area of atrophy of the central part of the fundus from which the immediate macular area is spared.

Case reports of four brothers, aged 27, 38, 44, and 46 years, with typical clinical pictures are presented and paintings of the fundus are included. All four had had night-blindness since childhood and progressive loss of vision. The older the patient, the more advanced was this loss of vision and the more complete was the retinal and choroidal atrophy. The author believes that this progression of the disease with age is a progression toward the typical picture of choroideremia and that actually these two diseases are the same.

Morris Kaplan.

Schulte, D. **Venous pulsations in the retina.** Klin. Monatsbl. f. Augenh. 113: 220-230, 1948.

Various existing theories concerning the cause of the venous pulsations in the eye disregard the fact that these pulsations appear as a rule only at the disc, but not in the periphery. Thin glial tissue alone covers the vessels in the disc and slight changes in pressure can, therefore, easily lead to pulsation. In the retina the nerve fibers prevent pulsation mechanically. Similarly, pulsation may be prevented whenever inflammation and edema lead to an increase of tissue within the disc. Anatomic structure and the level of the vascular bed determine the appearance of the venous pulse. Among 100 patients 36 percent had venous pulsation spontaneously and 31 percent after compression. Pulsation was lacking in 33 percent. In 33 patients there was a simultaneous arterial and venous pulse after compression. In one half of them the vein collapsed during the expansion of the artery and in the other half the movements were synchronous. Synchronous and alternating pulsation in the same eye in different venous branches was observed in three patients. Arteries and veins have a common sheath of tissue in the disc.   Max Hirschfelder.

Shelburne, S. A. **Retinal arteriovenous nicking: II A long term study of the development of arteriovenous nicking in patients with hypertension.** J. Lab. and Cl. Med. 33:1486-1487, Nov., 1948.

In 1939 the author's group reported their studies on the significance of various stages of retinal arteriovenous nicking in patients with hypertension before the Central Society for Clinical Research. They have now (1948) restudied some of the same patients after 8 to 10-year intervals and followed for the first time the development of this phenomenon from the first stage to the last. It was shown that the early lesion develops into the late lesion. Emphasis was placed on the importance of distinguishing these lesions, one from the other. Clear color drawings showing the various types of arteriovenous nicking and other retinal changes found in hypertensive patients accompanied the lecture.   F. M. Crage.

Sorsby, A., and Joll Mason, M. E. **A fundus dystrophy with unusual features.** Brit. J. Ophth. 33:67-97, Feb., 1949.

The authors record a study of five families in the members of which a genetic affection becomes manifest at about the age of 40 years. In the early stages there is edema and a hemorrhagic-exudative reaction in the central area of the retina which progresses to central atrophy with parietal sclerosis and heavy pigmentation. Ultimately the whole of the fundus becomes atrophic. The affection is inherited as a simple autosomal dominant. The study establishes the existence of a hemorrhagic type of macular dystrophy and confirms the view that dystrophies cannot always be regarded as localized lesions but are occasionally and possibly frequently merely the starting point of a diffuse retinal or choroidal disturbance. Gross pigmental disturbances are not always of infectious or toxic origin. The

earliest changes in a genetic affection may be hemorrhages and exudates identical in appearance with the lesions commonly observed in arteriosclerosis and metabolic disturbances. It cannot be definitely stated that cases of Doyne's choroiditis should not be included in this group. (51 figures, 24 in color.)

Orwyn H. Ellis.

Sorsby, A., and Ungar, J. **Intravitreal injection of penicillin: study on the levels of concentration reached and therapeutic efficacy.** Brit. J. Ophth. 32:857-864, Dec., 1948.

Since adequate therapeutic levels in the vitreous can now be obtained by subconjunctival injection, direct intravitreal injection of penicillin has become largely an academic question. In the experimental work it was found that adequate antibacterial levels persist in the vitreous for 36 and possibly 48 hours after direct intravitreal injection of 5,000 units of crystalline penicillin in water. In order to control infection it was necessary to start the treatment three hours or less after staphylococcos was introduced into the vitreous.   Orwyn H. Ellis.

Sorsby, A., and Ungar, J. **The control of experimental infections of the anterior chamber and of the vitreous by subconjunctival and retrobulbar injections of crystalline penicillin in doses of 1,000,000 units.** Brit. J. Ophth. 32:873-878, Dec., 1948.

Infections of the anterior chamber can be controlled, even after 24 hours, by subconjunctival injections of penicillin. Retrobulbar injections were less efficacious. The animals which were given penicillin 4 hours after the intravitreal injection of staphylococcus did well, whereas rabbits first treated 24 hours after infection did badly. In the vitreous infections the route of administration was of much

less importance than the time interval between the infection and the instigation of treatment.   Orwyn H. Ellis.

Vila Ortiz, J. M. **Intraocular pressure in cases of hemorrhage of the retina.** Arch. Ophth. **39**:661-664, May, 1948.

The incidence of low ocular tension, both physiologic and pathologic, is significantly greater in patients with hemorrhage of the retina than without. Low tonometric readings can be related to predominance of arteriosclerosis and high readings to predominance of phlebosclerosis.   Ralph W. Danielson.

Waldman, J. and Shannon, C. E. G. **Retinoblastoma (retinal glioma) cured by radon seeds.** Arch. Ophth. **41**:32-41, Jan., 1949.

This method was devised to overcome the difficulties that may occasionally be encountered in inserting radon seeds directly into the tumor or in applying them, embedded in dental stent, to the overlying sclera of the posterior part of the globe, as described by Stallard. Briefly, the method consists in the application of a thin, semipliable chromium-plated or rhodium-plated silver band applicator containing depressions in the distal end into which the required number of radon seeds fit. The length of the band depends on the location of the tumor as measured from a fixed point on the eyeball. This applicator follows the contour of the eyeball and is "buried" under Tenon's capsule and the conjunctiva. A patient with retinoblastoma in the remaining eye has been treated and observed for twelve years. She has been cured for nine years. The total of 3,104 r given was far below the dose advised by the fractionated method of Martin and Reese. The local use of radon by the method described is recommended as another form of treatment of this malignant disease, particularly when the exact and careful technic

of fractionated roentgenotherapy described by Martin and Reese is not available.   Ralph W. Danielson.

Weiss, C., Perry, I. H., and Shevky, M. C. **Infection of the human eye with cryptococcus neoformans (Torula histolytica; cryptococcus hominis).** Arch. Ophth. **39**: 739-751, June, 1948.

A case of infection of the human eye with cryptococcus neoformans is reported. The clinical diagnosis was "possible cyst of the retina with retinal detachment and uveitis." The sclera was trephined, and material obtained for culture showed the presence of this yeastlike organism. Injection of the culture into the anterior chamber of the rabbit produced visible pathologic changes as early as the fifth day. Histologic changes in the rabbit eyes are described. Characteristic was the formation of rosettes along the anterior surface of the iris and posterior surface of the cornea. The rosettes were composed of a central cryptococcus surrounded by a single row of polymorphonuclear cells and monocytes. The technique of culturing the organism in the anterior chamber of the rabbit may[3] contribute to the earlier diagnosis of this fatal disease.

John C. Long.

Winkler, G. **Fundus changes in hunger patients.** Klin. Monatsbl. f. Augenh. **113**: 231-234, 1948.

In two prisoners of war hunger induced disease characterized by debility and widespread edema. Visual disturbances developed and led to total amaurosis in one. Small, yellowish-white, sharply circumscribed spots were observed in the macular region similar to the spots in retinitis punctata albescens. (2 figures.)
                    Max Hirschfelder.

Witmer, R. **Retinal periphlebitis due to sarcoidosis.** Ophthalmologica **116**:288-290, Oct.-Nov., 1948.

After an unsuccessful cataract operation one eye of a patient with bilateral chronic uveitis had to be enucleated. The histologic changes in the anterior segment were probably related to the cataract operation and its sequelae. The retina contained tubercles of varying size, without caseation or hyaline degeneration. Without giving any other (clinical) evidence, the author considers these tubercles as a manifestation of Boeck's sarcoid.

Peter C. Kronfeld.

12
OPTIC NERVE AND CHIASM

Angius, T. **Papilledema following a thoracoplasty.** Rassegna ital. d'ottal., **17**: 342-354, Sept.-Oct., 1948.

Thoracoplasty was performed on a 24-year-old woman who developed a pulmonary tuberculosis after an acute influenzal infection. Ten days after the operation she noted severe headache, photophobia, and head sweating. Edema of the nervehead that produced a swelling of 3 D. in one eye and 2 D. in the other, retinal edema and numerous hemorrhages appeared. After a year, the fundi were entirely clear and the vision normal. The intracranial pressure was not elevated at any time.   Eugene M. Blake.

Duggan, W. F. **Use of vasodilators in syphilitic atrophy of the optic nerves.** Arch. Ophth. 39:645-656, May, 1948.

All of five patients with syphilitic optic nerve atrophy improved under intensive vasodilator therapy. None became worse. The improvement corroborates Kennedy's hypothesis that in syphilis angiospasm occurs in the arterioles of the central nervous system.

Ralph W. Danielson.

Eissler, Rolf. **Atrophy of the optic nerve due to malnutrition.** Arch. Ophth. 39:465-470, April, 1948.

The literature on the relation between vitamin deficiencies and optic nerve atrophy is briefly reviewed and two cases of visual disturbances in white men who were prisoners of the Japanese are reported in considerable detail. The visual difficulties were concurrent with other symptoms of vitamin deficiency and improved with an improvement in the diet.

John C. Long.

Fuchs, A. **Malignant retrobulbar neuritis.** Arch. Ophth. 41:60-64, Jan., 1949.

In three patients loss of vision and the light reflex, binocular in two, developed in two or three days, while the fundi remained normal. Later, primary atrophy of the papilla occurred, and, in spite of energetic treatment, there was not the slightest restoration of vision. For these reasons, this condition is termed "malignant retrobulbar neuritis."

Ralph W. Danielson.

Gát, L. **Toxic papilloretinitis as a typical ocular symptom in tuberculous individuals.** Ophthalmologica 117:43-50, Jan., 1949.

Among 10 to 15 per cent of the patients at the State Tuberculosis Hospital, the author discovered a characteristic form of neuroretinitis which he ascribes to tubercle bacillus toxin. The disease is mild and heals in 6 to 8 weeks. The ophthalmoscopic finding of a neuroretinitis was confirmed by corresponding histologic findings in three patients who died of pulmonary tuberculosis during the period of ophthalmologic observation.

Peter C. Kronfeld.

Jerome, B., and Forster, H. W., Jr. **Congenital hypoplasia (partial aplasia) of the optic nerve.** Arch. Ophth. 39:669-672, May, 1948.

Two cases of bilateral congenital hypoplasia of the optic nerve in otherwise normal eyes are reported. This anomaly

is ascribed to partial failure of development of the ganglion cell layer of the retina and a consequent deficiency of neural elements in the optic nerve. It must be differentiated from atrophy.

Ralph W. Danielson.

Kurz, O. **Papillitis arteriosclerotica.** Ophthalmologica **116**:281-285, Oct.-Nov., 1948.

The author describes two cases of a bilateral arteriosclerotic optic nerve disease characterized by sudden onset, papilledema of varying extent, abnormal circulatory and pulsatory phenomena in the retinal vessels, very low blood pressure in the retinal vessels (as revealed by dynamometry), marked ocular hypotony and rapid loss of vision. The outcome is bilateral optic atrophy of the primary type with atrophic excavation, narrowed and partly obliterated arteries, and amaurosis. These ocular findings are associated with severe arteriosclerotic, cardiac and cerebral changes. A few similar cases have been reported before.

Peter C. Kronfeld.

Moginier-Forel, A. **The treatment of optic neuritis with nicotinic acid.** Ophthalmologica **116**:304-306, Oct.-Nov., 1948.

The author does not consider the use of nicotinic acid the classical treatment for optic neuritis, but is glad to have it for those cases in which the usual treatment fails.   Peter C. Kronfeld.

Northington, P., and Rouen, R. L. **Optic neuritis and sinusitis.** U. S. Nav. M. Bull. **49**:101-103, Jan., 1949.

After recovery from the sinusitis with acute optic neuritis the visual fields, vision and optic nerve returned to normal.

Orwyn H. Ellis.

Reese, A. B. **Invasion of the optic nerve by retinoblastoma.** Arch. Ophth. **40**:553-557, Nov., 1948.

This study is based on the author's experience during the last 13 years. It is rare for the tumor to extend into the optic nerve beyond the lamina cribrosa for more than a few millimeters, and extremely rare for it to extend as far as 8 to 10 mm. The invasion begins in the cup around the central vessels. Extension into the nerve does not depend on the size of the tumor in the globe. When the tumor reaches the subarachnoid space, it spreads rapidly to the chiasm and the brain. In approximately 10 percent of the cases the tumor traversed the sclera and in 25 percent invaded the choroid where the cancer cells may enter the blood stream. On the basis of the arguments presented in this paper, there is no justification for the combined intracranial and orbital operation for retinoblastoma.

Ralph W. Danielson.

Salvi, G. L. **Retrobulbar optic neuritis from nutritional deficiency, a contribution to the war pathology of the eye.** Boll. d'ocul. **27**:654-665, Oct., 1948.

Four well observed cases of retrobulbar neuritis in repatriated war prisoners confirm the etiologic role of vitamin B_1 deficiency in these patients.

K. W. Ascher.

13

NEURO-OPHTHALMOLOGY

Cogan, D. G., and Loeb, D. R. **Optokinetic response and intracranial lesions.** Arch. Neurol and Psychiat. **61**:183-185, Feb., 1949.

In a series of 90 patients with cerebral disease the optokinetic response was abnormal in 58. With one exception, the optokinetic response was defective on rotation of the drum to the side of the lesion. It was the only ocularmotor abnormality in 26 patients and the only abnormality in the ocularmotor or ocular sensory system in 9 patients. Abnormality in the optokinetic response was most fre-

quent with lesions in the posterior or middle portion of the cerebrum, but was also found on occasion with lesions in the anterior portion. It was not dependent on involvement of the visual pathways. It was found associated with other signs in the following order: homonymous field defect, hemiparesis, nystagmus, deviation of eyes with closure of lids, alexia, motor aphasia and asterognosis. An abnormality in the optokinetic response is a frequent and valuable sign in the localization of cerebral disease but has no constant relation to the lateral lesions in the brain stem, cerebellum, or cerebellopontine angle. Theodore M. Shapiro.

Cohen, R., and Burnip, R. **Nevoid amentia**. Ann. West. Med. and Surg. **3**: 47-49, Feb., 1949.

The author reports an interesting case of a child with a large wine-colored hemangioma over the left half of the forehead and the entire region of distribution of the ophthalmic branch of the trigeminal nerve. A bilateral temporal pallor of the optic discs and esotropia, most marked on the right, were present. X-ray studies of the skull disclosed calcification which outlined the cerebral markings on the left side. Right hemiplegia, convulsions and a speech defect were also present. Orwyn H. Ellis.

Collins, R., and Bassenge, W. L. **The participation of the eye in infantile paralysis**. Klin. Monatsbl. f. Augenh. **113**: 255-260, 1948.

The authors examined 150 infantile paralysis patients during the Berlin epidemic of 1947. Eleven of the patients had a facial paresis, which was supranuclear in five of them. The prognosis of this facial palsy is relatively good. In two patients the seventh nerve was the only paresis evident in spite of typical findings in the spinal fluid. Other patients had ptosis, nine had abducens paralysis and five internal rectus paresis, some with facial palsy. Nystagmus and pupillary disturbances may be found in the cerebral cases. Papilledema and dilation of the retinal vessels is frequently found in the high-spinal and bulbar-pontine group. Four fifths of the "iron lung patients" showed these dilated vessels and half of them had edema of the papilla. The vision stays normal, the visual field is not contracted and the fundus findings regress after a few weeks. True optic neuritis was not observed, but is mentioned in the literature. Max Hirschfelder.

Crow, John. **A note on certain ocular phenomena of post-encephalitic Parkinsonism**. Glasgow M. J. **30**:29-34, Jan., 1949.

In 80 cases nystagmus was usually coarse and either horizontal or vertical. Diplopia was common and was usually associated with the nystagmus. Most of the patients had difficulty in opening or closing the eyes and attacks of rapid blinking. Unilateral or bilateral exophthalmus without hyperthyroidism was occasional. Horner's syndrome was never found. Oculogyric crises were present in 85 percent. One patient turned in a circle in oculogyric crises and the caloric test induced oculogyric crises in him.

F. M. Crage.

Fanta, H. **Opticochiasmatic arachnoiditis**. Klin. Monatsbl. f. Augenh. **113**: 246-255, 1948.

Two cases of arachnoiditis are described. One followed typhus and the other injury. In both there was reduction of vision and of the visual field, bilateral central scotoma, negative X-ray studies and meager neurological findings. Fever therapy which improves similar symptoms in retrobulbar neuritis did not influence the clinical picture. Headache is an important symptom. The optic nerve head may look normal or may show a

mild papilledema. Both patients improved temporarily after surgery. The literature of arachnoiditis in ophthalmology is surveyed and critically discussed.

Max Hirschfelder.

François, J. **The ocular manifestations of von Recklinghausen's disease.** Ann. d'ocul. **181**:753-791, Dec., 1948.

The basic symptoms include slowly progressive, multiple bodily subcutaneous and nerve tumors and pigmented areas, café au lait spots. Degenerative diseases in the nervous, osseous, and endocrine systems are frequently associated. The nerve tumors most frequently arise from the sheath of Schwann. Centrally, the most frequently involved areas are the acoustic nerve and the pituitary gland. Von Recklinghausen's disease is essentially a constitutional hyperplasia of undifferentiated ecto- and meso-dermal cells throughout the body. These foreign cells called "phakos" by Van der Hoeve are involved in several neuro-ophthalmo-cutaneous syndromes, including those of Bourneville, Hippel-Lindau, and Sturge-Weber-Krabbe. Every part of the eye and orbit may be involved in von Recklinghausen's disease except the lens and the lacrimal apparatus. The lids, orbit, and optic nerve are most frequently affected, and the conjunctiva and sclerocornea least frequently. In the lid the chord-like feel of the nerves is of some diagnostic importance. Extirpation of the tumors is not without danger because of hemorrhage. Optic nerve tumors may take the form of meningoblastomas, gliomas, and mixed tumors. Three cases are reported. In the first case which was clinically diagnosed as a uveal melanosarcoma, a Schwannoma of the ciliary body and sclera was seen in sections. The only other clinical sign was café au lait spots. In the second case progressive exophthalmus resulted from an orbital Schwannoma and in the third a Schwannoma of the conjunctiva coexisted

with large numbers of characteristic subcutaneous tumors and café au lait spots. (16 figures, 361 references.)

Chas. A. Bahn.

McKinney, J. McD., Mitchell, W., and Lisa, J. R. **Diplopia due to divergence insufficiency.** J. Nerv. and Ment. Dis. **108**: 507-510, Dec., 1948.

A metastatic carcinoma at the right cerebellopontine angle caused homonymous diplopia for distance but not for near, dizziness, headache, unsteadiness of gait, and nausea. The eyegrounds, visual fields, and extraocular movements were normal. Nine months later slight papilledema was noted. Necropsy revealed a hard white mass in the meninges that caused a marked pressure deformity of the pons and a large cystic cavity in the cerebellum. There were no demonstrable lesions in the region of the sixth nerve nuclei. Although no center of divergence is known, divergence insufficiency or paralysis is associated with a lesion of the posterior fossa.   R. Grunfeld.

Morone, G. **Pupillography in glare.** Boll. d'ocul. **27**:639-653, Oct., 1948.

Nine normal individuals were exposed to the light of a nonfrosted 500 Watt bulb yielding about 2820 lux at 1 meter. They had to fixate the light with one eye for 10 minutes to 1 hour while the fellow eye was bandaged. In some subjects, the eye to be exposed was covered for a preliminary period of between five and 20 days. Signs of fatigue of the iris were found both in the eye exposed to glare and in the covered fellow eye; in the latter it is explained by the consensual pupillary reaction. (9 pupillographic graphs, references.)   K. W. Ascher.

Morsier, G. de, and Balavoine, C. **Spasm of convergence.** Ophthalmologica **116**: 248-253, Oct.-Nov., 1948.

Eight cases of spasm of convergence associated with other neurologic disturb-

ances are reported jointly by an ophthalmologist and a neurologist. In seven of the cases head trauma was the cause, in the eighth an acute throat infection with ear complications. Four of the patients first showed ocular palsies of supra or infranuclear type and during the more or less complete recovery from the palsies the spasm of convergence developed. In all the patients the spasm of convergence could be brought on by movements of gaze, attempted or actually performed, in one specific direction. The spasm of convergence nearly always was a spasm of the near reflex, that is, accommodation and pupil were equally involved. There were neurologic sensory and motor signs of a unilateral cerebral lesion and turning the eyes toward the side of the lesion usually elicited a spell of convergence spasm. There was vestibular hyperexcitability of the central type. The authors are inclined to explain the convergence spasm as a "substitution phenomenon," that is a motor reaction executed by a supranuclear apparatus rather than a defective intentional motor reaction.   Peter C. Kronfeld.

Paufique, L., and Etienne, R. **Glioma and pseudoglioma of the chiasm.** Ophthalmologica 117:90-103, Feb., 1949.

In two of three cases of glioma of the chiasm which was suspected on the basis of clinical and roentgenologic findings the diagnosis was verified by surgical exploration. In one an autopsy revealed an astrocytoma. In the third case the findings at the surgical exploration were inconclusive. The authors assume a chronic inflammatory disease on the order of an arachnoiditis, possibly associated with an encephalitis.   Peter C. Kronfeld.

14

EYEBALL, ORBIT, SINUSES

Cox, R. A. **Proptosis due to neuroblastoma of the adrenal cortex (Hutchin-son's syndrome).** Arch. Ophth. 39:731-738, June, 1948.

Neuroblastoma of the adrenal gland with its subsequent metastases occurs almost entirely in children. It is of great interest to ophthalmologists because of its metastasis to the orbit, with resultant proptosis, discoloration of the lids and loss of vision. The orbit is invariably involved in the metastases, and frequently it is the eye which gives the first noticeable indication of the disease. The condition is highly malignant, and death usually occurs within three months after appearance of the first sign. A case of neuroblastoma is reported with autopsy findings in a 15-months-old-boy.

John C. Long.

DeVoe, A. G. **Fractures of the orbital floor.** Arch. Ophth. 39:595-622, May, 1948.

Lukens, reviewing the literature forty years ago, found 78 cases of traumatic enophthalmos and some nineteen hypotheses to explain its mechanism. It is now felt by most observers that of the factors enumerated only the direct and indirect fractures of the orbital wall are significant. Observation of 34 cases of fracture of the orbital floor suggest that the immediate care of such fractures will rarely be an ophthalmologic problem because of the multiplicity of accompanying injuries, often of a vital nature. A review of the literature reveals the measures most frequently used in immediate treatment. When weeks or months have elapsed the ophthalmologist is the one best fitted to carry out reparative work. Such repair may take the form of operation on the extraocular muscles or may require substitution of inert material in the orbital floor in order to restore orbital volume or to elevate the globe. In anophthalmos the appearance can often be improved by restoration of the orbital floor.

Ralph W. Danielson.

Neudörfer, A. **A rare case of injury to the orbit.** Wien. Klin. Wchnschr. **61**:76, Feb. 4, 1949.

Splinters of wood, which for over three years had caused a profusely discharging fistula of the right eye and whose removal had previously been attempted unsuccessfully at four different operations, were finally located and removed through a Krönlein orbitotomy. This operation had to be performed twice as only one piece of wood was taken at the first operation and a second fistula with one layer of many small splinters remained. There was no injury to the eyeball, muscles or nerves. B. T. Haessler.

Rupprecht, Hermann. **Albucid treatment of cellulitis of the orbit.** Klin. Monatsbl. f. Augenh. **110**:310-313, May-June, 1944.

Three patients with cellulitis of the orbit were given Albucid intravenously or intramuscularly. Prompt improvement and complete recovery followed in two patients; in the third abscess formation made an incision through the upper lid necessary. This patient too recovered, but was left with ptosis. George Brown.

15

EYELIDS, LACRIMAL APPARATUS

Cassady, J. V. **Dacryocystitis of infancy.** Arch. Ophth. **39**:491-507, April, 1948.

The author reviews 100 cases of dacryocystitis in infancy and reviews the literature in detail. He advocates probing of the nasolacrimal duct and irrigation of the sac and duct. Prolonged conservative treatment is a nuisance to both parents and the child, and is likely to result in permanent injury to the lacrimal passages. He works without anesthesia and uses a lacrimal cannula attached to a syringe instead of a probe.

John C. Long.

Firestone, Charles. **Prevention and relief of stenosis of lacrimal duct.** Northwest Med. **48**:111-112, Feb., 1949.

Early repair in post-traumatic epiphora is important for good function and a good cosmetic result. The author describes in detail a method which is always effective. A no. 3 lacrimal probe is inserted into the punctum, is pushed out through the duct opening of the duct on the lacerated surface of the lid, and then through the nasal portion of the duct into the sac. It is held in place by adhesive strips and is removed after seven days.

H. C. Weinberg.

Clarkson, Patrick. **Eyebrow repairs by thin deep grafts.** Guy's Hosp. Gaz. **67**: 256-258, Sept. 25, 1948.

Three methods are suggested. 1. A graft is cut from the temporal scalp. It is thin and takes evenly. 2. An area of upper temporal scalp is cut to eyebrow shape and size and the artery which enters its lower pole is dissected down to the ear, leaving a graft attached to a long arterial pedicle. A skin defect is established in the position of the missing eyebrow and the graft is tunneled into this position and sutured into place. 3. The use of a flap of hair-bearing scalp carried on a temporal or other pedicle. The pedicle is later returned leaving a flap of hair-bearing skin in the eyebrow region. A full thickness skin graft does not have to be rendered entirely free from subcutaneous fat to take well. Details of the technique of a thin deep free graft of hair-bearing scalp from the temporal area are presented.

Alston Callahan.

Fox, S. A. **Crescentic deformities of the lid margin.** Arch. Ophth. **39**:542-544, April, 1948.

A surgical method for the repair of crescentic deformities of the upper lid margin is presented. The involved portion of the lid, and the adjacent area of

the other lid are split. The tarsoconjunctival layers of both lids are then sutured together and a full thickness skin graft with hair from the region of the brow is sutured into the defect. The brow hair take the place of cilia. After a month the lids are separated.   John C. Long.

Kettesy, A. **Entropion in infancy caused by folding of the tarsus.** Arch. Ophth. **39**:640-642, May, 1948.

A case is reported.

Ralph W. Danielson.

La Rocca, Vito. **Implant of "Vitallium" tube in treatment of stenosis of the lacrimal duct.** Arch. Ophth. **39**:657-660, May, 1948.

The use of an implant is simpler and more effective than dacryocystorhinostomy. The technique is described.

Ralph W. Danielson.

Mildenberger. **Dacryoadenitis after dysentery.** Klin. Monatsbl. f. Augenh. **113**:268, 1948.

The author observed three cases of dacryoadenitis caused by dysentery. The course was favorable.

Max Hirschfelder.

Murphey, P. J., Newton, F. H., Stell, C., and Hawk, P. P. **Esthetic correction of unilateral anophthalmos by ophthalmoprosthesis.** Arch. Ophth. **40**:497-508, Nov., 1948.

From the results obtained in the esthetic correction of anophthalmos by the ophthalmoprosthetic technique in the cases reported, it is evident that growth of the cul-de-sac and the orbital area of the face may be stimulated, in a manner similar to the growth of muscle and bone associated with facial changes produced by orthodontic correction. Infants and children do not seem to experience any pain or discomfort during the period of construction and wear the prosthesis without being aware of its presence in the orbital socket.   Ralph W. Danielson.

Papolczy, F. **Purulent inflammation of the lacrimal canal caused by an accumulation of stony concretions.** Klin. Monastbl. f. Augenh. **113**:269-271, 1948.

After an unsuccessful tear sac extirpation purulent discharge persisted and was caused by ten stony concretions in the lacrimal canal, which had been overlooked. Single lacrimal stones are rare and multiple ones have not been described. Stones appear only in the lacrimal canal, never in the tear sac itself.

Max Hirschfelder.

Rössler, F. **A suture for entropion.** Klin. Monatsbl. f. Augenh. **110**:377-380, May-June, 1944.

Both needles of a double-armed suture with a glass head are inserted half way between the lid margin and lower orbital margin and between middle and temporal third of the lid, parallel to the lid margin and behind the orbicularis and brought out at the temporal orbital margin. Here the suture is tied over another glass bead. The suture is removed after eight days. Originally the operation was used for temporary relief, but the lid remained in good position even after removal of the suture.   George Brown.

Schindler, Rudolf. **Treatment of essential blepharospasm.** Klin. Monatsbl. f. Augenh. **110**:380-383, May-June, 1944.

The patients are asked to close their eyes as tightly as possible while looking down. After 2 to $2\frac{1}{2}$ minutes the muscle is exhausted and the patients readily open their eyes and keep them open for some time. Such exercises are applicable only in cases of psychoneurotic blepharospasm.   George Brown.

Sená, J., and Cerboni, F. **Hereditary and familial xanthomatosis.** Arch. de oft. de Buenos Aires 23:79-89, June, 1948.

There are various forms of xanthalasma: simple, as of the lids, multiple or eruptive tuberous, congenital or tumor-forming, and secondary. The first of these is the best known and occurs bilaterally, chiefly in women. This paper is concerned with the second, tuberous, form. Yellowish masses of varying size occur on the lids and in other parts of the body as well, and the disease is not limited to any age or sex. The authors analyse the hypercholesterinemia, which they consider the fundamental pathologic process of this disease, and describe its fate in the body. A detailed case report with photographs of the gross and microscopic lesions is given.   A. G. Wilde.

Spaeth, E. B., and Cappriotti, O. A. **Heteroplastic and isoplastic skin grafts.** Plast. and Reconstruct. Surg. 3:707-712, Nov., 1948.

Comments are made on heteroplastic and isoplastic grafts, and brief summaries are given of the few articles published on ectropion and its repair in ichthyosis congenita. In a fifteen-year-old boy with ichthyosis congenita ectropion began to develop at the age of eight. The condition has gradually become more severe and recently a corneal ulcer developed. Intermarginal lid adhesions were made, the lid defects prepared, and thromboplastic shellac was applied to the raw surfaces. Very thin free skin grafts from the thigh of a donor whose blood matched the patient's as to type, Rh, M and N factors were fitted into the defect. After a year the author reports successful takes. (4 figures.)   Alston Callahan.

Theodore, F. H. **"Silent" dacryocystitis.** Arch. Ophth. 40:157-162, Aug., 1948.

A mild type of dacryocystitis, usually mucoid, is often the cause of persistent conjunctivitis or tearing. This "silent" type of dacryocystitis is overlooked if investigation of the tear passages is limited only to a determination of patency. If the lacrimal washings are collected, the finding of mucus or frank pus containing pathogenic organisms will indicate the presence of "silent" dacryocystitis. Treatment, consisting largely of irrigations, results in cure of the dacryocystitis and conjunctivitis. This low grade mucous dacryocystitis may eventually lead to more obvious inflammatory changes in the lacrical passages.   John C. Long.

Toselli, C. **Elongation of the lacrimal canaliculi.** Rassegna ital. d'ottal. 17:334-341, Sept.-Oct, 1948.

Toselli reviews the literature and describes two cases of elongation of the inferior lacrimal canaliculi. In one the lids seemed stuck together at the inner angle so that they were reduced in length and height. Ptosis resulted. The border of the upper lid was normal, the lower showed a bowing, the cilia were normal and the lower canaliculus was definitely elongated. The second patient suffered from epiphora, had bilateral ptosis, epicanthus, paresis of the superior rectus of the left eye and a rudimentary caruncle. The lower canaliculus was twice the length of the upper.   Eugene M. Blake.

16

TUMORS

Bettman, J. W. **Treatment of malignant tumors of the retina.** Stanford Med. Bull. 6:437-443, Nov., 1948.

In about one of three cases of malignant tumor of the retina the lesion was unilateral. The average age of patients in this series in whom unilateral tumor was discovered was $3\frac{1}{2}$ years, of those with bilateral lesion it was $1\frac{1}{2}$ years and the prognosis is better in the former. Thorough ophthalmoscopic examination, with

a dilated pupil and under general anaesthesia, is most important in the first examination and in the monthly examinations of the sound eye.

When the lesion is unilateral immediate enucleation is definitely indicated and as large a piece of the optic nerve as is possible should be removed. The tumor is usually in an advanced stage. If a frozen section reveals neoplasm in the nerve, a radium implant is inserted but if the tumor has spread more than a few millimeters radiation is of doubtful value. If there is tumor in both eyes but only one quadrant or less and not the choroid is affected, in one eye, this eye is irradiated and the other eye is enucleated. If more is involved both bulbs are enucleated.

F. M. Crage.

Carpentdale, M. T. F. **Lymphosarcoma presenting as edema of the eyelids.** Lancet 1:305-306, Feb. 19, 1949.

Primary lymphosarcoma of the skin is very rare, although secondary lesions are not uncommon. A married woman, aged 61 years, was admitted to the hospital with a swelling about the left eye which was first noticed two weeks before and was slowly enlarging. Necropsy after ten weeks showed hemorrhage from ulcerated secondary growth in the stomach, and generalized lymphosarcoma. At first this patient was thought to have a recurrent facial cellulitis or periorbital cellulitis secondary to ethmoiditis. Other possible diagnoses were erysipelatoid and angioneurotic edema. A study of a biopsy specimen taken from indurated skin on the lateral margin of the left orbit suggested lymphosarcoma.

Theodore M. Shapira.

Dunnington, J. H. **Granular cell myoblastoma of the orbit.** Arch. Ophth. **40**: 14-22, July, 1948.

The histogenesis of myoblastoma, a type of tumor variously designated as myoblastic myoma, myoblastoma, rhabdomyoma and granular cell myoblastoma, is much discussed in the literature. It is believed by some to be a true neoplasm of immature, proliferating skeletal muscle cells (myoblasts) and by others to be a degenerative lesion. The author concludes that granular cell myoblastoma is a relatively common tumor and widely distributed throughout the body. Its occurrence in the orbit is rare and two cases are reported. The tumors presented no characteristic clinical picture, and the differential diagnosis was purely histologic. One was malignant although the tumor is more commonly benign.

Ralph W. Danielson.

Grom, E. **Modified epithelioma of the lacrimal gland.** Arch. d'opht. **8**:593-610, 1948.

Grom reports four cases of epithelioma of the lacrimal gland, three in men of 21, 29, and 32 years, and one in a woman of 32 years. He reviews the subject of lacrimal gland tumors, with particular reference to the so-called mixed tumor, and points out that histologically the gland is similar to the salivary glands and may be simultaneously involved. Clinically these tumors are of varying malignancy; some evolve slowly over many years while others are rapidly invasive and penetrate the nasal sinuses and the brain. Metastases are rare. In all cases the epithelium is the principal tissue involved. It is disposed in canalicular-acinous, acino-canalicular, or atypical formation. Parenchymatous changes are generally fibrous but myxomatous plaques are common. The author suggests that the name "épithélioma remanié," or "modified epithelioma," is to be preferred for this type of tumor. P. Thygeson.

Jorio, S. **Congenital epibulbar tumors.** Rassegna ital. d'ottal. **17**:289-303, Sept.-Oct., 1948.

Two cases of bilateral dermoids are reported. In the first case the father of the patient, a five-year-old boy, had congenital ptosis of the right upper lid and a mass on the temporal side of each globe which resembled a dermoid. The dermoids on the boy's eyes were very extensive and were removed surgically. The other patient, a 19-year-old boy had bilateral dermoids, pre-auricular malformations, irregular dentition, facial asymmetry, underdevelopment of the mandible, deafness, mental retardation and a coloboma of the upper lip. The pathology of dermoids is discussed. (8 figures.)

Eugene M. Blake.

Posner, M., and Horrax, G. **Tumors of the optic nerve.** Arch. Ophth. **40**:56-76, July, 1948.

Failure of vision in one eye combined with some degree of exophthalmos, together with a normal visual field and visual acuity in the other eye in a patient with no other evidence of an intracranial lesion, strongly suggests the diagnosis of a tumor of the optic nerve within the skull. Three cases of intracranial tumor of the optic nerve with survival from four and one-half to twelve years are reported. The prognosis is not as consistently poor as is generally believed.

Ralph W. Danielson.

Stansbury, F. C. **Lymphosarcoma of the eyelid.** Arch. Ophth. **40**:518-530, Nov., 1948.

The literature is reviewed, lymphosarcoma is discussed, and a case is reported, not because it represents a rare tumor, but for its unusual features. The lesion was considered an atypical, low grade inflammatory process by all who examined the patient, and the disease progressed rapidly to a fatal termination in forty days. The neoplasm in this case is unique because of the meager amount of involvement of the lymph nodes and the rapid,

destructive spread to all the viscera and other tissues of the body. Less than one percent of all lymphosarcomas originate in the region of the eye.

Ralph W. Danielson.

17

INJURIES

Burch, E. P. **Treatment of common eye injuries.** Northwest Med. **48**:104-107, Feb., 1949.

A careful history is essential for diagnostic, therapeutic, and medicolegal considerations. Examination of the deeper structures is important irrespective of how trivial an eye injury may appear externally. Local anesthesia is important in obtaining coöperation during the examination but cocaine is avoided. Tetanus antitoxin should be used cautiously. For deep wounds of the eye the author advises penicillin (300,000 units) immediately, and the next day a typhoid-paratyphoid vaccine (15 to 25 million) intravenously. The penicillin and typhoid are given alternately at least three to five times and sulfonamides are often given concurrently. Removal of all hopelessly blind, damaged eyes is suggested because of the danger of sympathetic disease. Wounds of the sclera and cornea and methods for their repair are reviewed. The complicating cataract, glaucoma and iritis and their therapy are discussed. Irrigation with a solution of 10-percent neutral ammonium tartrate is suggested for lime burns after all lime particles have been removed with an applicator impregnated with vaseline.

H. C. Weinberg.

Boshoff, P. H., and Jokl, E. **Boxing injuries of the eyes.** Arch. Ophth. **39**:643-644, May, 1948.

Ten cases of ocular injury due to blows incurred in boxing are recorded. There were hemorrhages, cyclodialysis, retinal tears, retinal detachment and kerato-

conus. Boxers deliberately try to produce head injuries.   Ralph W. Danielson.

Clothier, W. L. **Treatment of extra-ocular foreign bodies.** Northwest Med. **48:** 107-109, Feb., 1949.

Foreign bodies under the upper lid produce more pain than do the uncomplicated foreign bodies of the cornea. Severe corneal damage may occur when an untrained person attempts to remove what is really a pigmented mole of the iris. It is important to examine the puncta, lid margins, superior retrotarsal fold and upper and lower lids as well as the cornea in looking for foreign bodies. Adequate anaesthesia should be used. The use of a sharply pointed instrument is preferred to the spud and burr. In the removal of iron rust particles it is noteworthy that overzealous removal of stained tissue in the central corneal area often reduces vision more than if a small stained area had been left alone. It is important that vision be recorded before treatment is begun and when the patient is discharged. (1 table.)
. H. C. Weinberg.

Stuart, Jean. **Clostridium welchii infection of the eye.** Brit. M. J. p. 272, Feb. 12, 1949.

Although the patient received 300,000 units of penicillin every three hours after an unsuccessful attempt to remove a piece of intraocular steel, the eye became septic and proptosed and had to be enucleated. During the operation gas and blood-stained pus escaped freely. From the pus a pure growth of Clostridium welchii was obtained. Penicillin fails to diffuse into the vitreous in appreciable quantity.
                            F. Grunfeld.

18

SYSTEMIC DISEASE AND PARASITES

Appelmans, M., and van Vooren, H. **The eye manifestations of myasthenia gravis.** Ophthalmologica **117:**8-18, Jan., 1949.

In a girl, 8 years of age, with myasthenia gravis the mimic musculature of the face and the extraocular muscles were predominantly involved.
                        Peter C. Kronfeld.

Bruce, G. M. **Changes in the ocular fundus associated with pheochromocytoma of the adrenal gland.** Arch. Ophth. **39:**707-730, June, 1948.

Pheochromocytomas are tumors growing from cells of the so-called chromaffin system. The dominant finding in cases of this tumor is vascular hypertension, in the course of which pathologic changes may be found in the retina or in its blood vessels or both. The findings cannot be differentiated ophthalmoscopically from those encountered in hypertensive vascular disease. Treatment consists of the surgical removal of the tumor. Three cases in children, all with pathologic changes in the retina, are reported.
                            John C. Long.

Cross, A. G. **Ocular disturbances associated with malnutrition.** Tr. Ophth. Soc. U. Kingdom **66:**102-104, 1946.

No gross impairment of night vision was demonstrable with a Livingston rotating hexagon in 119 prisoners liberated from camps in Siam of whom 17 had nutritional amblyopia. They were always hungry and most of them had had malaria, dysentery, pellagra and beriberi. Burning of the feet often preceded the blurred vision which could be relieved by nicotinic acid, but the diet evidently contained sufficient vitamin A to maintain normal night vision.
                        Beulah Cushman.

Esente, I. **Further ophthalmologic observations upon tuberculous meningitis treated by the Cocchi method.** Rassegna ital. d'ottal. **17:**318-333, Sept.-Oct., 1948.

Cocchi's treatment of miliary tuberculosis and tuberculous meningitis consists of the use of streptomycin, sulfone and vitamins A and D2. Esente reports upon the lesions and treatment in 150 cases and reports 85 percent greatly improved. He discusses the ocular involvement under five headings: 1. symptoms of ordinary functional disturbances, such as photophobia, ocular hyperesthesia and amaurosis; 2. symptoms of the extrinsic ocular muscles, paralysis, contracture, and nystagmus; 3. the intrinsic muscles and pupillary changes; 4. orbital affections and exophthalmos; and 5. ophthalmoscopic changes. Miliary tuberculosis of the choroid, disturbances of intrinsic and extrinsic muscles and early stages of tuberculous meningitis are benefited by streptomycin therapy.

Eugene M. Blake.

Fraser, J. D. **Ocular disturbances associated with malnutrition.** Tr. Ophth. Soc. U. Kingdom 66:96-98, 1946.

The author, a prisoner in the internment camp of Hong Kong, states that the diet was rich in carbohydrates and deficient in fats, proteins, salts and vitamins. It was associated with a syndrome characterized by edema, neuritic symptoms, a syndrome of subacute combined degeneration of the cord, mental disturbances, skin lesions, variations in blood pressure, prolonged diarrhea, dysentery, chronic malaria and diphtheria. Of 246 patients with visual complaints the cornea was involved in 119, corneal dystrophy was present in 64, retrobulbar neuritis in 43, retinitis in 2, and a central retinochoroiditis in 4. Chronic retrobulbar neuritis with partial optic nerve atrophy was noted in 174 patients. Beulah Cushman.

Grammatico, A. D. **Pneumothorax and intraocular tension.** Arch. de oft. de Buenos Aires 23:90-91, April-June, 1948.

Pneumothorax can bring about hypertrophy of the right ventricle. No coincident change in ocular tension immediately after the introduction of the air, or several hours later, could be demonstrated. A. G. Wilde.

Haynes, H. A., Jr., and Parry, T. L. **Alopecia areata associated with refractive errors.** Arch. Dermat. and Syph. 59:340-342, March, 1949.

In 61 patients with alopecia areata there was a rapid regrowth of hair in three months after the continuous wearing of glasses and no recurrence as long as the error was adequately corrected. The predominant error was a small astigmatism at an oblique axis. F. H. Haessler.

Hobbs, H. E. **Ocular disturbances associated with malnutrition.** Tr. Ophth. Soc. U. Kingdom 66:116-122, 1946.

The author discusses the data on 200 men with reduced visual acuity associated with central scotoma. Temporal pallor was common; a few patients had general pallor of the disc and attenuated blood vessels, a few had some pigmentary disturbance between the fovea and the optic disc and in eight there was macular damage. Visual fields were constricted in only those most severely affected. All were debilitated and many had suffered from several of the diseases endemic in prison camps, malaria, beriberi, famine edema, pellegra, and dysentery, and 37 had lesions of the nervous system. No clear relationship to a single disease was apparent but marked improvement occurred when animal protein was added to the diet. Beulah Cushman.

Livingston, P. C. **Ocular disturbances associated with malnutrition.** Tr. Ophth. Soc. U. Kingdom 66:19-44, 1946.

The author reviews the effect of starvation on the eyes of 3,000 Royal Air Force personnel repatriated from Japanese

prison camps after 2½ years. Defects of central vision with scotoma were found in 200. Peripheral contractions were recorded and a loss of perception established at rod level. In some patients the corneoscleral border zone was invaded by vascular loops. Grave corneal lesions were not found and the vitreous appeared normal. Degenerative changes of the retina could be seen in the macula. There were fine discrete white spots and pigmentary disturbances and the most common finding was the loss of the foveal reflex. It was often impossible to find the macula and between the macula and disc a glistening silver-gray sheet could be seen. Temporal pallor of the disc was very common and in some there was complete atrophy. There was often a wide discrepancy between the visual acuity and the appearance of the disc and the macula. Results of treatment were often better than expected.   Beulah Cushman.

Lockwood, J. H. **Reiter's disease, Behcet's syndrome and Stevens-Johnson disease; a study and comparison.** U. S. Nav. M. Bull. **49**:41-49, Jan., 1949.

The author completely reviews the literature and the manifestations of each of these conditions of obscure etiology in turn and compares their symptoms.

Orwyn H. Ellis.

Lyle, T. K. **Malnutritional amblyopia.** Post Grad. M. J. **24**:649-655, Dec., 1948.

Malnutritional amblyopia which occurred in prisoners of war in the far east is a different entity than retrobulbar neuritis. Predisposing factors are excessive manual labor and intercurrent disease. The lesion is probably a disease of the macular capillaries, bilateral, and of gradual onset. The 5° to 10° central scotoma is not dense and has sloping edges and may disappear with early treatment. The fundus may be normal, in the early stages, or have dilated veins and some

edema. In later stages, the disc may be normal or slightly pale.

Irwin E. Gaynon.

Philps, A. S. **Ocular disturbances associated with malnutrition.** Tr. Ophth. Soc. U. Kingdom **66**:99-102, 1946.

The author reports on three patients with atrophy of the optic nerve after returning from the internement camps. All had beriberi, malaria, or dysentery. The smoking of the crude strong local tobacco was thought to have some influence, as the amblyopia was indistinguishable from that due to tobacco.

Beulah Cushman.

Ridley, Harold. **Ocular disturbances associated with malnutrition.** Tr. Ophth. Soc. U. Kingdom. **46**:45-70, 1946.

The author reports on the eye findings of several hundred persons in Rangoon and Singapore who had been imprisoned by the Japanese in Siam, Malaya and N.E.I. and who had suffered varying degrees of starvation for three and a half years. Most men lost much weight, and some reached an extreme degree of emaciation. Nutritional diseases due to deficiency of vitamin B were common. There was less evidence of lack of vitamins A, C, and D. There were many manifestations of dry and wet beriberi. One percent of the men had impairment of vision of two to three years duration. None complained of hemeralopia. About one half of those with amblyopia had beriberi. The visual failure was accompanied by nerve deafness in many cases and in some by ataxia. No amblyopia was found among the relatively few women that were seen though their food had been little better than that of the men. Deficiency of accommodation was almost universal among released prisoners.

Beulah Cushman.

Shapland, C. D. **Ocular disturbances as-**

sociated with malnutrition. Tr. Ophth. Soc. U. Kingdom 66:77-95, 1946.

The author describes the ocular manifestations found among the prisoners of war in Singapore from 1942 to 1945. Among 975 patients 777 had refractive errors and no organic disease, 104 had had retrobulbar neuritis, 45 had a history of visual disturbances during captivity and now had temporal pallor of the discs, normal vision and no scotoma, and 49 had other ophthalmic diseases.

Beulah Cushman.

Smith, D. A. Ocular disturbances associated with malnutrition. Tr. Ophth. Soc. U. Kingdom 66:111-116, 1946.

The author discusses amblyopia in the inmates of a civilian camp in Hong Kong from 1942 to 1945 in relation to intake of the main nutrients, to incidence of other nutritional diseases, and to certain other extrinsic factors. There were 1,300 men, 900 women and 300 children under 16 years of age. Loss of body weight was about 26 percent. No extrinsic toxic or infective factor was found common to all, except nutritional deficiency. Thirty patients developed amblyopia who were at the time under treatment with daily injections of synthetic vitamin B, for beriberi. The provision of foods rich in B complex, soya beans, rice polishings and camp brewed yeast prevented progressive deterioration. An amino-acid may have been the missing factor.

Beulah Cushman.

Stannuss, Hugh S. Ocular disturbances associated with malnutrition. Tr. Ophth. Soc. U. Kingdom 66:123-126, 1946.

Many years ago the author correlated the ophthalmologic syndrome that is part of beriberi and pellagra and recent studies have made no change. It is an optic neuropathy which belongs to the group of deficiency syndromes and it may be due to

dysfunction of the capillaries supplying the neurophyl of the lateral geniculate body.   Beulah Cushman.

Streiff, E. B. The ocular symptomatology of the posterior cervical syndrome. Ophthalmologica 116:292-297, Oct.-Nov., 1948.

The syndrome of Barré-Baertschli comprises a number of ill-defined forms of ocular discomfort and asthenopia caused by a chronic arthritis in the region of the third to fifth cervical vertebra.

Peter C. Kronfeld.

19

CONGENITAL DEFORMITIES, HEREDITY

Dekking, H. M. Toxoplasmosis as a cause of congenital defects. Ophthalmologica 117:1-7, Jan., 1949.

The clinical and histologic eye findings in an infant with toxoplasmosis are reported in detail. One eye had a pseudocoloboma of the macula, the other a lesion like the congenital falciform detachment of the retina. The clinical diagnosis of toxoplasmosis was based on a positive neutralization test of the infant's blood and on the presence of multiple typical foci of calcification in the brain. Histologic examination of the brain revealed typical foci of toxoplasmosis containing the parasite. Toxoplasmosis may also cause microphthalmos, congenital cataract, and congenital total retinal detachment.

Peter C. Kronfeld.

Lloyd, R. I. Clinical course of ocular complications of arachnodactyly. Arch. Ophth. 40:558-569, Nov., 1948.

Observations on 21 patients over periods of 5 to 14 years and on 25 others for shorter periods have convinced the author that arachnodactyly is not always a nonprogressive, congenital defect but often a true abiotrophy. The disease is inherited as a dominant in many families and as a

recessive in others. A parent with normal eyes and some of the skeletal defects may transmit the disease in complete form. In eyes with good vision the course is uneventful and not progressive but the prognosis is poor when vision is not good because of associated progressive changes in the uvea and the tendency to complete dislocation of the lens and retinal detachment. Six case reports are given.

Ralph W. Danielson.

Rehsteiner, K. **Another Swiss family with hereditary retinitis pigmentosa.** Ophthalmologica 117:51-59, Jan., 1949.

Rehsteiner reports the pedigree of 70 members in four generations of a Swiss family of whom 16 had retinitis pigmentosa, 33 had normal eyes and 21 could not be examined. The transmission definitely followed the dominant mode. Visible fundus changes were present before any loss of function could be demonstrated.   Peter C. Kronfeld.

20

HYGIENE, SOCIOLOGY, EDUCATION, AND HISTORY

Aragañaraz, Raúl. **Impressions on an educational voyage through the United States, Canada and England.** Arch. de oft. de Buenos Aires 23:71-78, April-June, 1948.

The author observed the ophthalmologic facilities of the United States, Canada and Great Britain for four months. He contrasts the combined theoretical and clinical teaching in the United States, where student enrollment is limited to the available facilities, with conditions in Argentine where instruction is theoretic, the number of students unlimited and one professor may be required to teach five hundred simultaneously. The great cost of American medical education is surprising. In London the work of Dallos interested him especially. He is

perfecting a contact lens which is used without fluid. Small openings in the glass allow the intervening space to become filled with tears.   A. G. Wilde.

Ballantyne, A. J. **Johannes Evangelista Purkinje.** Tr. Ophth. Soc. U. Kingdom 66:503-543, 1946.

Only one or two copies of the collected works of Purkinje, which embody his contributions to clinical ophthalmology, are available. There is a photostatic copy in the Surgeon General's Library in Washington. Purkinje, born in Bohemia in 1787, is a physiologist of the senses who stands at the turning point between Goethe's age of poetry and the Platonic contemplation of nature, and the purely scientific Aristotelian era of Johannes Müller. He was professor of physiology in Breslau but it was in his own house under most unfavorable circumstances that Purkinje laid the foundation of modern physiology. He became the principal of the first physiological laboratory in 1839, and, oddly, after this time he published no discovery of first rate importance.

He was a pioneer in the description of most of the subjective visual figures, notably those obtained by galvanic stimulation, recurrent images, entoptic appearances from the shadows of retinal vessel, the dependence of brightness of color upon intensity of light, the choroidal figure, the rosettes of light produced by use of digitalis, and the peculiar radiation following the instillation of belladonna. In clinical medicine, Purkinje was the first to study the vertigo and rolling of the eyes produced by rotating the erect body in the vertical axis. He described an optometer, explained the diffraction of light from a bright object, described the manner in which the field of vision may be measured, used the blind spot to determine the place of entrance of the optic nerve, and explained how the radius of

curvature of the cornea and sclera and the prominence of the eyeballs may be measured. He described the Purkinje's images formed by the anterior and posterior surface of the cornea and the anterior and posterior surfaces of the lens. He described the transparency of the cornea and drew attention to the arcus senilis. He noted the blueness of the sclera in infants, and pointed out that change in the transparency of the aqueous or vitreous could be determined by oblique illumination. He described in detail the iris, the reactions of the pupil, and the response of the latter to belladonna and hyoscyamus.

Beulah Cushman.

Burian, H. M. **The history of the Dartmouth Eye Institute.** Arch. Ophth. **40:** 163-175, Aug., 1948.

The origin of what in 1937 became the Dartmouth Eye Institute dates back to 1919, when Ames and Proctor began their research on the optical properties of the eye. The author describes the various policies and factors that ultimately resulted in the closing of the Institute. In the short span of its existence, the Dartmouth Eye Institute has made lasting contributions to the study of visual physiology. A complete bibliography of the papers published by the members of the Institute is appended.   John C. Long.

Fralick, F. B. **Emergency eye care in general practice.** J. Michigan St. M. Soc. 47:1365-1369, Dec., 1948.

The author describes the best treatment for some of the most common ocular emergencies. Removal of a foreign body from the cornea is recommended and describes in detail. Contusions with subluxation of the lens or hemorrhage are discussed and the possibility of glaucoma and corneal staining causing a loss of vision are emphasized. In the treatment

of lacerations of the lids the importance of obtaining smooth union of the lid border is emphasized. Lacerations of the lateral or medial canthi should be sutured with heavy chromic catgut (4-0) in order to prevent epiphora and to avoid additional plastic surgery. Chemical burns of the eye should be copiously irrigated with water whether due to alkali or acid. (2 figures.)

Herman C. Weinberg.

Imus, H. A. **Testing vision in industry.** Tr. Am. Acad. Ophth. pp. 261-273, Jan.-Feb., 1949.

The relative merits of the ortho-rater, sight-screener, telebinocular and clinical tests are compared in a series of industrial patients. In most of the tests, the ortho-rater was somewhat superior.

Chas. A. Bahn.

Kuhn, H. S. **An eye physician reports on the Ninth International Congress of Industrial Medicine, London, England, September 13-17, 1948.** Indust. Med. **18:** 33-36, Jan., 1949.

In the "National Health Service" the ophthalmologist gets $800 a year for 46 weekly three-hour sessions at a hospital clinic. The maximum allowance is eight sessions a week if he can get them, the average is two. For 60 refractions a week he gets 100 pounds, is allowed to work 46 weeks a year and can earn $18,400 very easily.

This unusually lucrative position has been brought about mainly by the opticians who fought hard to refuse to concede important parts of the program desired by the government.

Surgical fees were not investigated. Hospitals shortages are very great, there is a backlog of six to seven month's surgery, those who can afford to, push themselves ahead and this results in delayed service for the poor.

The author has unlimited praise for

English cordiality, and she experienced no antagonism to Americans.

F. M. Crage.

Matthews, J. L. **Use of absorptive lenses: facts for the profession.** Tr. Am. Acad. Ophth. pp. 274-277, Jan.-Feb., 1949.

The retina is protected from abiotic radiation in the normal eye. Ordinarily, individuals exposed to sunlight in sports require no ultra-violet filter glasses. In industry, specific filters are recommended by the Government. Except by prolonged contact as in glass blowers the moist surface of the cornea reasonably protects the eye from infrared radiation. The normal eye under ordinary conditions has no need for mildly tinted lenses. Tinted glasses worn habitually lessen the wearer's tolerance to glare. Green glasses aggravate the defects of protanomalous persons. In industry lay safety men should be carefully instructed in the fundamentals of light filtering lenses.   Chas. A. Bahn.

Verhoeff, F. H. **American ophthalmology during the past century.** Arch. Ophth. 39:451-464, April, 1948.

This historical article deals with the development of the specialty in the United States. Not one ophthalmological contribution of major importance has originated in the United States but American ophthalmologists have made many contributions of minor importance and a few of considerable importance.

John C. Long.

Vila Ortiz, J. M., and Granados, E. **Legal aspects of obstructions of the central retinal artery.** Arch. de oft. de Buenos Aires 23:94-100, April-July, 1948.

A study of the relation between degrees of exertion and general arterial tension, pressure in the central artery of the retina, and ocular tension can give results of practical value. An obstruction in any vessel may have been brought on by exertion which caused occlusion of the disturbed circulation by an unknown mechanism.   A. G. Wilde.

Zobel, W. A. **Initial results of eye testing program.** Tr. Am. Acad. Ophth. pp. 277-279, Jan.-Feb., 1949.

In a visual and safety study involving 14 ordnance plant group jobs, the percentage of injury is compared in workmen with adequate and inadequate vision. A difference of 20 percent was found.

Chas. A. Bahn.

PAN-AMERICAN NOTES

Edited by MANUEL URIBE TRONCOSO, M.D.

Contributions should reach the editor before the 12th of the month

ARGENTINA

THE IV ARGENTINIAN CONGRESS OF OPHTHAL-MOLOGY

This meeting, held in Mar del Plata, December 13 to 18, 1948, was a great success and was attended by ophthalmologists from all parts of the Western Hemisphere. The official subjects were "Ocular blastomas" and "The surgical treatment of strabismus." The former subject was divided into 14 parts and Dr. Algernon Reese of New York was invited to give the section on "Treatment of bilateral blastomas with X rays." Dr. Jorge Malbran presented the second official subject. Dr. Magin A. Diaz and Dr. Joaquin A. Caretti read a paper on "The prevention of blindness in the quinquenal plan of the secretariat of public health."

Courses were given during the meeting by the following ophthalmologists: Dr. Moacyr E. Alvaro, Dr. Raul Argañaraz, Dr. Archimedes Busacca, Dr. Ramón Castroviejo, Dr. Federico C. Cerboni, Dr. Baudilio Courtis, Dr. Carlos Garbino, Dr. Alfredo D. Grammático, Dr. Gunther von Grolman, Dr. Waldemar Niemeyer, Dr. Justo Lijó Pavia, Dr. Robert Pereira, Dr. Paulina Satanowsky de Neumann, and Dr. José A. Sená.

SOCIEDAD DE OFTALMOLOGIA DE CORDOBA

Newly elected officers of this society elected to serve during 1949 are: President, Dr. Roberto Obregón Oliva; secretary, Dr. Alberto Urrets Zavalia (hijo); treasurer; Dr. Roque A. Maffrand; 1st elder, Dr. Rodolof Laje Weskamp; 2nd elder, Dr. Marcos H. de Anquin.

BRAZIL

SÃO PAULO SOCIETY

The prize of the Sociedade de Oftalmologia de São Paulo for 1948 was awarded to Dr. Drino Coelho who read a paper on "Glaucomatous Syndromes."

At the joint meeting of this society with the Centro de Estudos de Oftalmologia in July, 1948, Prof. Julio Szymansky read a paper on "Keratoplasty and the demi-Elliot operation method" (demonstration on patient) and Dr. A. Busacca read one on "Clinical and anatomical observations on perivasculitis of the nodular type seen in cases of chorioretinitis." At the August, 1948, meeting Prof. Ernst Simonsen spoke on "Effects of the degree of illumination and of color upon fatigue."

CELEBRATES ANNIVERSARY

The Ophthalmologic Clinic of the Escola Paulista de Medicina celebrated its 12th anniversary in March, 1949. The occasion was marked by several special scientific meetings.

ORTHOPTIC COURSE

The second course in orthoptic training opening in May, 1949, and given by the assistants of the ophthalmologic clinic of the Escola Paulista de Medicina, could be attended by graduates in medicine, trained nurses, and social workers.

PAN-AMERICAN ASSOCIATION OF OPHTHALMOLOGY

Resolutions adopted by the Committee on Inter-American Medical Relationships in Havana, January, 1948, were:

1. For the most widespread understanding of the scientific papers presented, it is recommended that:

a. An abstract of a paper to be presented must be transmitted to the proper authorities at least six months in advance of a congress so that lantern slides of a translation may be made and shown simultaneously with the presentation of the paper. In order to provide funds for this purpose it is recommended that the fee for the IV Congress be increased to $25.00.

b. The use of recorded discs for the immediate translations or discussions to be tried.

c. All members of the Pan-American Association of Ophthalmology be urged to become bilingual for Spanish and English or Portuguese and English.

2. In the interest of closer relationships between the ophthalmologists of the Western Hemisphere, the facilities of the Pan-American Association of Ophthalmology should be utilized for the introduction of accredited members when traveling. Be it understood that any member will be welcome as a visitor to the hospitals and scientific meetings of the members resident in the city visited. Be it understood also that the resident member should not be responsible for the social entertainment of any such visiting members. It is suggested that visiting members (a) be furnished with a distinctive badge with name and address and (b) be furnished with an interpreter if necessary.

3. It is recommended that during the first three days of the Pan-American Congress, social luncheons be arranged to bring together resident members and members from the different countries.

4. It is recommended that, since the center of medical education and research has passed from Europe to the Western Hemisphere, the Pan-American Association of Ophthalmology use its full facilities for rapid interchange of information of interest to its members.

5. It is recommended that a fund be established to be known as the Pan-American Fund, which

will grant fellowships for traveling in different countries.

PERSONALS

Dr. Federico K. Cramer of Buenos Aires visited São Paulo, Brazil, from March 12 to 18, 1948. Dr. Cramer read a paper at the Sociedade de Ophthalmologia de São Paulo entitled "Technical difficulties and complications of dacryocystorhinostomy by the external method." On March 15 he gave the inaugural lesson for the 1949 class in ophthal-

mology of the Escola Paulista de Medicina. His subject on that occasion was "Physiopathology of the corneal tissue."

Dr. Juan Vicente Echague, Montevideo, Uruguay, and Miss Maria Ribeiro and Dr. Paunessa, Buenos Aires, have been taking orthoptic training under the direction of Miss Lygia Alves Lima, orthoptic technician of the Centro de Estudos de Oftalmologia in São Paulo. Dr. Echague hopes to organize an orthoptic training center in Montevideo.

NEWS ITEMS

Edited by DONALD J. LYLE, M.D.
601 Union Trust Building, Cincinnati 2

News items should reach the editor by the 12th of the month

DEATHS

Dr. Wayne Bernard Granger, Emporia, Kansas, died December 26, 1948, aged 56 years.

Dr. William F. Hardy, St. Louis, Missouri, died May 4, 1949.

ANNOUNCEMENTS

PRERESIDENT TRAINING COURSE

The faculty of the College of Physicians and Surgeons of Columbia University have approved plans to enlarge the preresident training course (formerly given as basic science for the residents of the Institute of Ophthalmology and allied hospitals) so that up to 15 applicants who have received or have been promised appointments in institutions approved by Columbia University will be accepted for four months' full-time training at the Institute of Ophthalmology.

Anatomy, embryology, pathology, physiologic optics, bacteriology, pharmacology, physiology, biochemistry, and refraction will constitute the basic studies upon which further studies preparing the matriculants for training in ophthalomolgy will be founded. The course will start January 2, 1950. Applications must be submitted before November 1st to the office of the assistant dean in charge of Graduate Medical Education, 630 West 168th Street, New York 32, New York.

ORTHOPTIC TECHNICIANS EXAMINATION

All applications for the annual examination of orthoptic technicians to be conducted by the American Orthoptic Council must be received by the office of the secretary, Dr. Frank D. Costenbader, 1605 22nd Street, N.W., Washington 8, D.C., by July 1st, and must be accompanied by the examination fee of $25.

BOOKS AND PERIODICALS NEEDED

The National Committee for Chile is now receiving gifts for the library of the Medical School of the University of Chile at its new collection center,

Room 318, in the Library of Congress, Washington, D.C. Periodicals, books, and reference materials of the Medical School were totally destroyed in the recent fire. Urgently needed are medical periodicals of the last 10 years and recent medical books.

DE SCHWEINITZ LECTURE

The 12th annual de Schweinitz lecture, sponsored by the Section on Ophthalmology, College of Physicians of Philadelphia, will be given on Thursday, November 17, 1949, by Dr. Arthur J. Bedell of Albany, New York. The subject of Dr. Bedell's address will be "The macula in the aged."

MISCELLANEOUS

GILL GRADUATE COURSE

The Gill Memorial Eye, Ear, and Throat Hospital has just finished its 22nd annual spring graduate course. There was a registration of 250 doctors from all parts of the United States and Canada. On the faculty were: Dr. Banks Anderson, Dr. H. W. Brown, Dr. W. B. Clark, Dr. W. P. Dearing, Dr. W. W. Eagle, Dr. Harold Falls, Dr. E. P. Fowler, Jr., Dr. N. B. Herman, Dr. L. P. Garrod, Dr. Glen G. Gibson, Dr. C. L. Jackson, Dr. Carl C. Johnson, Dr. A. C. Jones, Dr. Harold H. Joy, Dr. Louis Paufique, Dr. Peter N. Pastore, Dr. Bernard Samuels, Dr. E. W. Scheldrup, Dr. Albert E. Sloane, Dr. Claire L. Straith, Dr. A. Earl Walker, Dr. Henry Williams, Mr. L. A. Watson, and Dr. John S. Lundy.

The next course will be given beginning April 3, 1950.

GLASGOW GRADUATE LECTURES

During May, a series of lectures were held in the Department of Ophthalmology, University of Glasgow. On May 4th, Prof. W. J. B. Riddell spoke on "European vacation." Dr. Fergus Campbell discussed "Pupillary movements," on May 11th; Dr. Antionette Pirie read a paper on "The structure of the vitreous humor," on May 18th; and, on May 25th, Dr. W. O. G. Taylor spoke on "Bleeding and clotting within the eye."

Societies

A.O.S. meeting

Papers presented at the 85th annual meeting of the American Ophthalmological Society, held at The Homestead, Hot Springs, Virginia, June 2nd, 3rd, and 4th were:

"Late fistulazation of operative wounds: Diagnosis and treatment," Dr. John H. Dunnington, New York, and Dr. Ellen F. Regan (by invitation); "Simultaneous bilateral malignant ocular melanoma," Dr. Frederick C. Cordes, San Francisco, and Dr. Robert Cook (by invitation); "Nevus flammeus associated with glaucoma," Dr. Harold H. Joy, Syracuse, New York.

"Goniotomy and the treatment of congenital glaucoma," Dr. Harold G. Scheie, Philadelphia; "Spontaneous cysts of the ciliary body simulating neoplasms," Dr. Algernon B. Reese, New York; "Clinical and experimental investigations on para-amino-salicyclic acid (PAS) and streptomycin in ocular tuberculosis," Dr. Trygve Gundersen, Boston, and Prof. G. B. Bietti (by invitation).

"Sarcoid involving the orbit," Dr. F. N. Knapp, Duluth, Minnesota; "The psychology of the poor reader," Dr. William H. Crisp, Denver; "Iris pigment flakes on the posterior surface of the cornea following cataract extraction," Dr. Walter S. Atkinson, Watertown, New York; "Lamellar keratoplasty: Technique and results. Comparative study with penetrating keratoplasties and keratectomies," Dr. Ramon Castroviejo, New York.

"Ocular conditions associated with idiopathic hyperlipemia," Dr. Edwin B. Dunphy, Boston; "Oblique muscle surgery from the anatomical," Dr. Walter H. Fink, Minneapolis; "Fat embolism of the retina: A clinical and pathologic report," Dr. Arthur G. DeVoe, New York; "Retinitis punctata albescens," Dr. Arthur J. Bedell, Albany, New York.

"Cataract surgery routine in India," Dr. Raynold N. Berke, Hackensack, New Jersey: "Temporal arteritis (The Horton-Magath-Brown syndrome) as a cause of blindness: Review of the literature and report of a typical case," Dr. Gordon M. Bruce, New York; "Intraocular diktyoma and glioneuroma," Dr. F. Bruce Fralick, Ann Arbor, Michigan, and Helenor Campbell Wilder (by invitation).

"How we can best study primary glaucoma?" Dr. Eugene M. Blake, New Haven, Connecticut; "Experimental and clinical use of aureomycin in herpes simplex," Dr. Alson E. Braley, New York; "Tonometry: The variation of ocular rigidity in chronic glaucoma and an adaptation of the Souter tonometer," Dr. Searle B. Marlow, Syracuse, New York; "Clycloelectrolysis for galucoma," Dr. Conrad Berens, New York, and Dr. Benjamin L. Sheppard and Dr. Arthur B. Duel, Jr., (by invitation).

Midwestern Research meeting

The midwestern section of the Association for Research in Ophthalmology held its organizational meeting in the Elliott Auditorium, Oscar Johnson Institute, St. Louis, Missouri, on Saturday, March 26th. Dr. William F. Hughes, Jr., was elected chairman; Dr. William Howard Morrison, vice-chairman; and Dr. T. E. Sanders, secretary and treasurer.

The following scientific program was enjoyed by 65 ophthalmologists from Ohio, Indiana, Illinois, Wisconsin, Minnesota, Iowa, Nebraska, Kansas, and Missouri.

"Some possible applications of 'spreading factor' in ophthalmology," Dr. Philip Shahan, and W. A. Moor, A.B., Washington University; "A family of idiopathic flat detachment of the macula: Question congenital," Dr. Harold F. Falls, University of Michigan; "Motor imbalances and the fusional processes: A preliminary report," Dr. Kenneth N. Ogle, Mayo Clinic; "Cortical potential changes in amblyopia ex anopsia," Dr. Edward Bierman and Dr. Dallas Dyer, St. Louis University; "The effect of the pupil on flicker fusion fields: Preliminary report," Dr. Paul Miles, Washington University; "Antistine: A study of its toxicity on topical applications to the eye," Dr. T. F. Schlaegel, Jr., Indiana University; "Some ocular effects of sympatholytic compounds," Dr. Frank W. Newell, Dr. William L. Ridgeway, and Dr. Robert W. Zeller, Northwestern University; "Beta irradiation: An evaluation of a radium-D applicator for ophthalmic use: Preliminary report," Dr. Fred M. Wilson, University of Illinois.

Second Western Research meeting

The second annual meeting of the Western Section of the Association for Research in Ophthalmology was held on March 25th at the University of California Medical School, San Francisco. On the program were the following papers.

"The correlation of clinical and histopathologic findings in vernal conjunctivitis," Dr. N. M. Biegelman, University of Southern California; "Tonus of the extraocular muscles: An electromygraphic study," Dr. R. M. Flanagan, Dr. B. Kvernland, and Dr. R. V. Hill, University of Oregon; "Some experimental studies on corneal transplants," Dr. A. E. Maumenee, Stanford University; "Dynamic muscle balance: Part I. Theory and technique; Part II. Some applications and results," Dr. L. Bond and Dr. Kenneth C. Swan, University of Oregon; and "Clinical experiences with vitreous replacement," Dr. G. P. Landegger, University of Southern California.

At the dinner meeting, John B. deC. M. Saunders, F.R.C.S., librarian of the Medical School Library, professor of anatomy and lecturer in medical history and bibliography of the University of California Medical School, gave the address of the evening. His subject was "Some aspects of the activities of the central nervous system."

Alabama Academy organized

At the Jefferson Davis Hotel in Montgomery, Alabama, on April 20th, the Alabama Academy of

Ophthalmology and Otolaryngology was organized. The meeting was called by Dr. Harvey Searcy of Tuscaloosa, and Dr. Bruce Holding of Montgomery was appointed temporary chairman. Fifty-two men from all over the state were in attendance.

Officers were elected as follows: Dr. Frank Clements, Birmingham, chairman; Dr. Phil P. Gilchrist, Mobile, chairman elect; and Dr. Karl B. Benkwith, Montgomery, secretary and treasurer.

During the scientific session, Dr. John Lingo, Mobile, read a paper on "Allergy in otolaryngology," and Dr. John Keyton, Dothan, spoke on "Hormone therapy in cataracts."

BROOKLYN PROGRAM

At the 108th regular meeting of the Brooklyn Ophthalmological Society, the following brief case reports were presented: "Retinitis pigmentosa with drusen on the optic nerve," Dr. Regina V. Gilroy; "Sarcoidosis with corneal involvement," Dr. Mary G. Bruno; "Angioid streaks," Dr. A. Benedict Rizzuti; "Severe erythema multiforme bullosum with ocular complications: Treated with aureomycin," Dr. Leo Esbin; "Optic neuritis as a complication of chicken pox," Dr. Mortimer Cholst; "Sympathetic ophthalmitis," Dr. Joseph Mandelbaum; "Epithelial invasion of the anterior chamber," Dr. Morris H. Pincus; "Oxycephaly," Dr. Martin Bodian.

MILWAUKEE GUEST SPEAKER

Dr. Otis S. Lee, Department of Ophthalmology, University Hospitals, Iowa City, Iowa, spoke at the April 26th meeting of the Milwaukee Oto-Ophthalmic Society. The subject of his lecture was "Cyclodialysis."

PENNSYLVANIA ACADEMY MEETING

Dr. George M. Coates, Philadelphia, was guest of honor at the annual meeting of the Pennsylvania Academy of Ophthalmology and Otolaryngology held at Harrisburg, April 22nd to 24th. Dr. Coates spoke on "Reminiscences in otorhinology."

Other speakers were: Dr. John R. Lindsay, Chicago, "Vertigo: Differential diagnosis and treatment," and "Eustachian tube obstruction: early diagnosis and treatment"; Dr. Ralph O. Rychener, Memphis, "External diseases of the eye: Treatment and diagnosis"; Dr. C. Stewart Nash, Rochester, New York, "Functional diseases of the nose," and "The otolaryngologic consultant in compensation and liability actions"; Dr. Albert D. Ruedemann, Detroit, "Beta ray uses in ophthalmology," and

"Medical treatment of early cataract"; Dr. Ralph R. Pino, Detroit, "Economics of ophthalmology"; Dr. Arno E. Town, Philadelphia, "Fibrin closure of surgical wounds"; Dr. Harrison F. Flippin, Philadelphia, "Recent advances in chemotherapeutics."

In addition to these papers a round-table discussion on "Headache" was held, and Dr. Ruedemann and Dr. Town conducted a study club on cataract problems.

Specialists from all parts of Pennsylvania, as well as from surrounding states, attended the meeting. Officers elected for the following year were: President, Dr. Daniel S. DeStio, Pittsburgh; president elect, Dr. Jay G. Linn, Pittsburgh; secretary, Dr. B. F. Souders, Reading; treasurer, Dr. Bruce A. Grove, York.

GUEST LECTURERS AT WEST VIRGINIA

Guest lecturers at the meeting of the West Virginia Academy of Ophthalmology and Otolarygology held at Martinsburg on May 13th and 14th were: Dr. Glen G. Gibson, Temple University, Philadelphia; Dr. Walter Klingman, University of Virginia, Charlottesville; Dr. G. Slaughter Fitz-Hugh, University of Virginia, Charlottesville.

Among the papers presented were: Dr. William Stone, Jr., "The Stone-Jardon implant"; Dr. Glen Gibson, "Medical and neurologic ophthalmology"; Dr. Walter Klingman, "Pain mechanisms associated with headache"; Dr. James K. Stewart, Wheeling, "Penicillin in acute otitis media"; Dr. G. S. Fitz-Hugh, "Treatment of facio-maxillary fractures"; Dr. Charles T. St. Clair, Bluefield, and Dr. Ben W. Bird, Princeton, "Allergic manifestations of the eye."

PAN-AMERICAN-N.S.P.B. MEETING

At a recent meeting of the officers of the Pan-American Association of Ophthalmology and of the National Society for the Prevention of Blindness, it was decided to have a joint meeting of the two organizations in Miami Beach, Florida, March 26 to 30, 1950.

For the National Society for the Prevention of Blindness, this would be their annual meeting; for the Pan-American Association of Ophthalmology, this would be an interim meeting, inasmuch as the next Congress of the Pan-American Association of Ophthalmology will be held in Mexico City early in 1952.

The headquarters of this joint meeting will be at the Floridian Hotel, Miami Beach, Florida. Summer rates will prevail.

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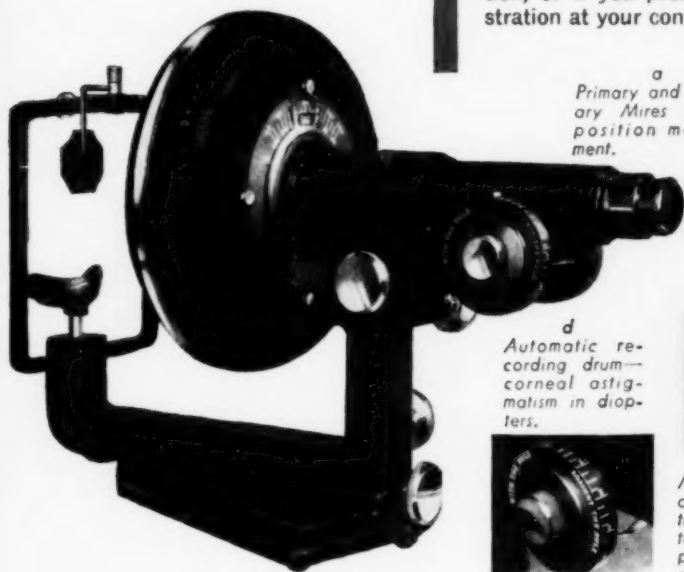
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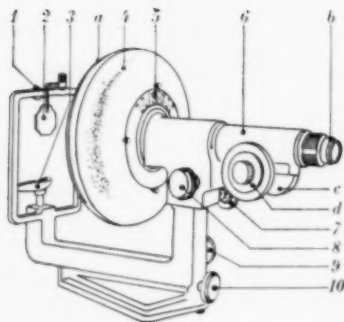
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Proctor Medal Award

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of the

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Seventeenth Meeting

Chicago, Illinois

June 21 and 22, 1948

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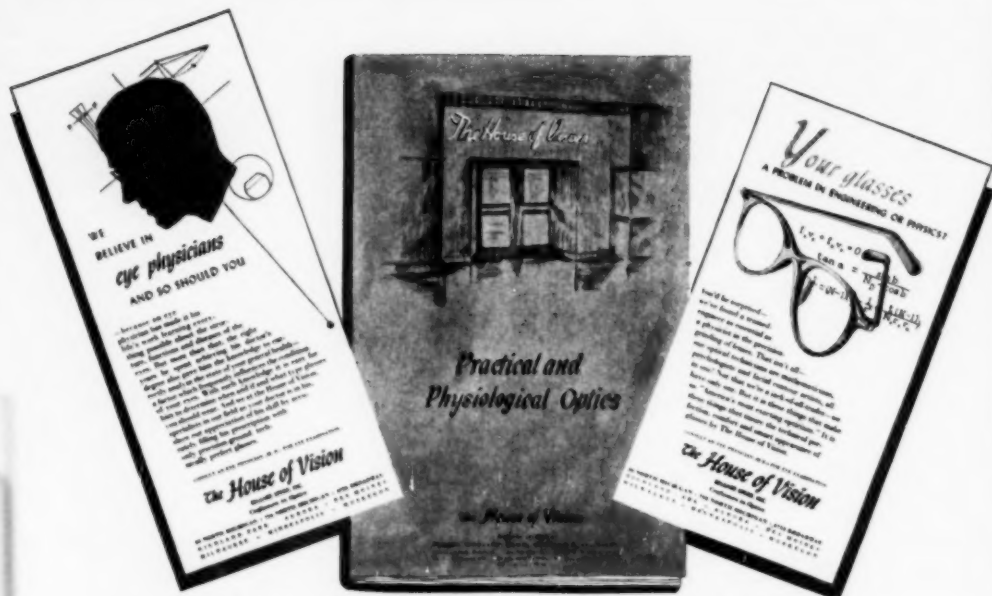
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CONTENTS

THE
PROCTOR
MEDAL

Funds for the establishment of the Research Medal of the Association for Research in Ophthalmology were donated in 1947 by Mrs. Francis I. Proctor of Santa Fe, New Mexico, as a memorial to her late husband. Dr. Proctor, a Boston ophthalmologist, became intensely interested in the experimental side of ophthalmology after his retirement, and participated in numerous studies on the etiology and treatment of trachoma. The purpose of the medal is to stimulate research and to honor investigators who have made notable contributions in the basic fields of ophthalmology. The medal is to be awarded without regard to the nationality or professional status of the recipient.

*   *   *

THE JONAS S. FRIEDENWALD
PROCTOR MEDAL AWARD
PROCEEDINGS
of the seventeenth meeting of the
Association for Research in Ophthalmology
Chicago, Illinois, June 21 and 22, 1948

*   *   *   *

JONAS S. FRIEDENWALD

A SHORT BIOGRAPHY OF DR. JONAS S. FRIEDENWALD

Dr. Jonas S. Friedenwald was born in Baltimore, June 1, 1897, the son of the distinguished ophthalmologist, Dr. Harry Friedenwald, and Bertha Stein Friedenwald. He received his early education at Calvert and Friend's schools in Baltimore; entered The Johns Hopkins University in 1913, where he was graduated with honors in 1916. He entered The Johns Hopkins University, School of Medicine, in 1916, and was graduated with a distinguished record in 1920. Thereafter, he became house officer in medicine in The Johns Hopkins Hospital (1920-21) and, in 1921-22, studied eye pathology under Dr. Frederick Verhoeff, receiving an M.A. degree in pathology from Harvard University in 1922.

He then went to Philadelphia, where for one year he studied in the out-patient department of the University and Wills Hospitals under Dr. de Schweinitz and Dr. Zentmayer. In 1923, he returned to Baltimore and since then has been associated with his father, Dr. Harry Friedenwald, in the practice of ophthalmology.

Although in active practice, Dr. Friedenwald did not abandon his interest in pathology and research. He took over the subdepartment of ophthalmic pathology in the Department of Pathology of The Johns Hopkins University, School of Medicine, under the late Dr. George MacCallum. With the founding of the Wilmer Institute in 1925, Dr. Friedenwald was appointed instructor in ophthalmology in charge of the pathological division. Here his flair for investigation found full opportunity for expression. His earlier work was chiefly in ophthalmic pathology, culminating in the publication of his textbook in 1928. During this period he became interested in the problem of the mechanism of the intraocular secretion, an investigation which since then has been his major work. However, his work was not confined to this field alone. His mathematical mind has led him into various physical problems, the results of which are the slitlamp ophthalmoscope, his theory of the relationship of intraocular pressure and ocular rigidity, the standardization of tonometers, and so forth. It is, however, in the broad fields of ophthalmic pathology and physiology that Dr. Friedenwald has made his major contributions.

He was appointed associate in ophthalmology in 1929, and associate professor in 1931, which position he now holds. Dr. Friedenwald is now in full charge of the pathological and physiological laboratories of the Wilmer Institute, and of the glaucoma research program.

Dr. Friedenwald received the Research Medal of the American Medical Association in 1935, and the Howe Medal of the University of Buffalo in 1948. He now is the recipient of the Proctor Award.

REMARKS ON ACCEPTANCE OF THE PROCTOR AWARD

June 21, 1948

Dr. Adler and Dr. Thygeson have left me quite speechless for the moment. Not that such embarrassment is unpleasant. It feels wonderful to have such things said about you even when you know they are untrue. I am reminded of the story about a Viennese artist whom a lady asked to paint a portrait of her husband.

"When can your husband sit for me?" asked the artist.

"Never," said the lady. "He is dead."

"Can I see a photograph?" the artist asked.

"I have none," answered the lady, "but I will describe him to you."

Noticing the look in the lady's eyes, the

artist concluded she was a bit cracked and, to pacify her, agreed to paint a picture according to her description. Two weeks later the lady came for the unveiling, and the artist wondered how she would react to his efforts. She sat before the picture and, as he removed the covering cloth, her face was enraptured. Finally she stretched out her hands toward to portrait and said, "August, how beautiful you are!—But how you have changed!"

If I may for the moment consider this award impersonally, I would like to suggest that the establishment of this award—not the choice of the present recipient—the flourishing state of this association, and the high caliber of its program, all indicate the increasing importance of basic research in ophthalmology.

Professor Northrop of Yale has pointed out in a recent book that every science goes through two phases. There is first what he calls the natural history phase of science in which facts are gathered and classified, the phase of taxonomy. In our science that phase is represented by the classification of ocular diseases, differential diagnosis, descriptive anatomy, morphologic pathology.

Northrop points out that when sufficient facts have been gathered in the natural history phase of a science, attempts are begun to place these facts in a rational order. This Northrop calls the mature phase of the science. In ophthalmology this phase is concerned with questions of etiology, pathogenesis, physiologic mechanisms.

Naturally, especially in the biologic sciences, the natural history phase of the subject is never done. There are still new distinctions to be made in the classification of disease, new disease pictures to be described. I do not wish to imply any disparagement to clinical research. The point is that the field of strictly clinical investigation has been so thoroughly harvested that really great effort, wisdom, and experience are required in order to make a genuinely new contribution to that field. Such a contribu-

tion is an achievement of high order. Its author has accomplished something much more difficult than did the illustrious fathers of clinical ophthalmology who in the 1860's and 1870's discovered a new disease at least once a month.

The point that I wish to make is not that clinical investigation is to be disparaged. It is, on the contrary, to be greatly admired, but its gleanings in the well-harvested field are few and far between.

By contrast the field of basic research is rich and ripe for the harvest. The slogan of our association should not be that basic research is recondite, solemn, austere,—but that it is easy, joyous and exciting. The orchard is full of golden fruit. One can hardly take a step without discovering something new and illuminating.

The natural history phase of a science requires increasing specialization. The taxonomists in different fields have little need of one another. Often their languages become mutually incomprehensible. In the mature phase of a science the interrelations of allied fields become, on the contrary, increasingly important. This means that there must be institutions within the framework of which men with different backgrounds of training can work and think together in intimate association. The work which has been cited for the current award would not have been possible but for the facilities supplied by The Johns Hopkins Medical School and its Department of Ophthalmology, the Wilmer Institute. I find it a little startling to realize that I have been working the same stall for a quarter of a century. I think that is an unduly long time, and wonder why they don't fire me. The reason why I don't resign is simply that I have the best job in the ophthalmological world.

But men are more important than institutions, and it has been my signal good fortune in the work which your committee has cited for the award to have had a series of collaborators who were really outstanding. I cannot mention all of them but there was, first

of all, Petey Pierce, a professional physiol-
ogist with a genius for instrumentation.
Then came Bob Stiehler, a biochemist,
trained by Mansfield Clark, an excellent ex-
perimenter with a really profound analytical
grasp of thermodynamics, who called me
down severely whenever I made a mistake
in thermodynamic reasoning. Then there was
Heinz Herrmann, trained in biochemistry
by Linderstrom Lang of Copenhagen.

Herrmann is almost unique among bio-
chemists in his understanding of the role of
structure in the biochemical and physiologi-
cal process, in his realization of how much is
lost from the biological system when tissue
is ground up into a soup for the purposes of
chemical extraction. Then there was Wil-

helm Buschke, whom I think most of you
know, who is now in charge of the research
laboratory at the Manhattan Eye and Ear,
after having worked shoulder to shoulder
with me for seven years. Finally there is the
youngest in the series, Bernie Becker, who
came to work with me only a year ago and
who will some day be an ophthalmologist of
distinction. Each one of these has contrib-
uted to our work not merely industry and
enthusiasm, but brilliant insights of con-
ception or interpretation. Insofar as the
work which your committee has cited merits
consideration for the award that you have
given it, the credit is theirs as much as mine.
I thank you in their name as well as in my
own.

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THE FORMATION OF THE INTRAOCULAR FLUID*

PROCTOR AWARD LECTURE OF THE ASSOCIATION FOR RESEARCH
IN OPHTHALMOLOGY

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I met Dr. Proctor only once, and only briefly, but I formed the impression of him then as a gentle and deeply kind person whose interest in the science of ophthalmology was one of abiding devotion. It is a fitting memorial to his quiet but persistent zeal that an award should have been established by this association in his name. I am very proud and happy to be the recipient of this award, and I am deeply grateful to the association for this honor.

Knowledge of the mechanism of control of intraocular pressure is basic to any interpretation of the pathogenesis of glaucoma, and knowledge of the mechanism by which fluid and dissolved substances are transported into and out of the eye is important in any understanding of the metabolism of the lens. It is no wonder, then, that work in this field has engaged the attention of a great many investigators, and that the literature is voluminous and confusing. I shall not attempt a comprehensive review but shall merely outline those contributions of others, the interpretation of which constitutes the logical basis for my own point of attack.

One large group of investigators has approached the problem by studying the chemical composition of the aqueous, and the relations of this composition to that of the blood. The early results in this field, particularly those of Duke-Elder,[13] lent themselves to the conclusion that the composition of the aqueous resembles that of a dialysate of the blood plasma.† Duke-Elder and others concluded that the aqueous was in diffusional exchange with the blood plasma across a barrier whose chief relevant characteristics, like that of the capillary wall, were its impermeability to colloids and its permeability to crystalloids.

Later studies with the aid of more exact and refined techniques have shown that the chemical composition of the aqueous is not exactly that of a dialysate of the blood plasma. There are definite and important discrepancies. Nevertheless, the overall resemblance is approximately true, and the existence of some diffusional exchange between blood and aqueous may be accepted as thoroughly established. There is, indeed, a very strong a priori reason for expecting this to be true because, in the iris at least, the capillaries expose their naked walls to the intraocular fluid.

It follows that fluctuations in capillary blood pressure and in the osmotic composition of the blood would be expected to reflect themselves in fluctuations in intraocular pressure. Abundant experimental confirmation of these expectations has been presented by Duke-Elder[12] and by others. What is remarkable, however, is that persistent changes in blood pressure or in the osmotic pressure of the plasma colloids cause very

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† The theory of membrane equilibria was developed by Donnan[11] in 1911, and its application to biologic systems was fully worked out by Van Slyke[57] in 1922-1925. In applying this theory to the blood-aqueous problem, Duke-Elder, in 1927, left bicarbonate out of account. With this omission Duke-Elder calculated that the Donnan factor, that is, the ratio of aqueous sodium to plasma sodium and of plasma chloride to aqueous chloride, should be 0.84, although this value had previously been shown by Van Slyke to be approximately 0.95. Duke-Elder's experimental data agreed with his erroneous value for the Donnan factor. If the experimental data are correct, the aqueous is very far indeed from a dialysate of the plasma. For further analysis of these discrepancies see Meyer.[40,41]

little persistent effect on intraocular pressure. Some of the discrepancies and even paradoxes in this field have been emphasized, particularly by Robertson,[42] and it is plainly apparent both from experimental studies and from ordinary clinical experience that there are local compensating mechanisms which play important roles in the regulation of intraocular pressure, and that simple diffusional exchange between blood and aqueous merely furnishes the background, the important background, upon which these local mechanisms operate.

The existence of some diffusional exchange between blood and aqueous does not justify the conclusion, sometimes drawn, that the aqueous is or must be stagnant. It has been supposed, for instance, that if the aqueous were not stagnant, and if fluid were filtered into the ocular cavity from some bed of capillaries of higher than average pressure, the larger molecules of the solutes would be held back by the filtering boundary, and that a measurably hypotonic aqueous would result.

Since the aqueous is not measurably hypotonic, Magitot[38, 39] and others have concluded that it is stagnant. This conclusion is erroneous. If a solution is filtered through a barrier of sufficiently small pore size to retard the transport of the larger solute molecules, an osmotic pressure difference immediately arises on the two sides of the filtration boundary, retarding the movement of water relative to the solutes. Consequently the osmotic pressure difference between filtrate and mother liquor cannot be greater, and generally is much less than the effective filtration pressure.

It is easy to calculate, for instance, that a filtering mechanism yielding aqueous 1 percent hypotonic in electrolytes as compared with the plasma would require a filtering pressure in the capillaries of over 100 mm. Hg. So far no investigator has claimed that his measurements, for instance, for sodium or chloride in the aqueous are accurate within 1 percent, nor, in fact, that the ex-

pected composition of a dialysate of the plasma could be estimated within that degree of accuracy. Within the present limits of the experimental data, therefore, no assertion that the aqueous is stagnant is justified.

The only conclusive way to find out whether the aqueous circulates or is stagnant is by a direct measurement of the water flow. An effort which I made in this direction many years ago led to an estimate of through and through circulation in dogs' eyes of one cubic mm. per minute.[16] Kronfeld,[37] using a similar technique, reached the same estimate. More recent studies by Kinsey and Grant[34, 33] on the rate of exchange of solutes between blood and aqueous were found by them to be compatible with a flow of four cubic mm. per minute in the rabbit. It is gratifying that such widely differing experimental approaches led to estimates of the same order of magnitude.

The early chemical studies on the composition of the aqueous as noted above showed that, in a rough and approximate fashion, the aqueous resembles a dialysate of the plasma. With more modern and more nearly exact studies, discrepancies have appeared and it has become increasingly clear that many factors other than simple diffusional exchange play a part in the picture. Davson and Weld,[10] in their most recent studies, have found that the dog's aqueous is hypertonic in crystalloids by about 2 percent. Benham, Duke-Elder, and Hodgson[3] have extended these results. Similar findings are reported by Roepke and Hetherington.[43] Scholz and Wilde,[44, 50] using radio-sodium, found even more marked discrepancies in guinea pigs. Kinsey and Grant, however, do not find an excess of electrolytes in the aqueous of rabbits.

From their osmotic studies, Duke-Elder and Davson concluded that the aqueous is a secretion, or, more precisely, that electrolytes are secreted into the aqueous. This conclusion may indeed be true since, as will appear below, it is in accord with arguments

reached from quite different consideration.

The experimental data presented by Duke-Elder and Davson do not, however, in themselves justify this conclusion, for some water must be lost from the aqueous by evaporation through the cornea.[48] At least a part of the hypertonicity of the aqueous is to be attributed to this loss of water, but no quantitative data are available with which to estimate the magnitude of this effect. It is not certain, therefore, that any measurable hypertonicity would remain if losses by evaporation were eliminated.

Glucose has been shown by many investigators to be present in the aqueous at a lower concentration than in the plasma. The deficit is of the order of magnitude of 20 percent. No definite conclusions can be drawn from this finding as to the mechanism of formation of the intraocular fluid since the deficit in glucose could well be accounted for by local consumption. Adler[1] has demonstrated how large a factor local consumption can be by his analysis of the distribution of glucose in the vitreous, which indicates that the closer one gets to the retina, the lower the glucose concentration.

Recent studies by Kinsey and Grant[34] reveal that levulose, a sugar of the same molecular size as glucose and one which is surely less actively consumed by the intraocular tissues, is present in the aqueous in no greater concentration relative to the plasma than is glucose. Urea is another non-metabolized, nonelectrolyte that has been much more extensively studied than levulose. This is found in the aqueous in concentrations about 30 percent lower than in the plasma. Urea (molecular weight, 60) is a much smaller molecule than levulose (molecular weight, 180). Weld, Feindel, and Davson[49] found that the blood-aqueous barrier is almost impermeable to raffinose (molecular weight, 504), and Swan and Hart[46] found the barrier normally impermeable to inulin (molecular weight, 5,000). These are all un-ionized, not metabolized, water soluble, lipoid insoluble substances. The general rule would appear that their transfer into the aqueous is retarded relative to electrolytes, and that the relative retardation is greater the larger their molecular size.

It would be natural, at first sight, to attribute the retardation of these substances to a filtering process. As noted above, however, the hypotonicity of a filtrate when computed in osmotic units cannot be greater than the effective filtration pressure. Several authors, particularly Kinsey and Grant, have explored the plasma-aqueous distribution of urea at artificially high plasma urea levels, and have reached figures for the aqueous deficit in urea that would require capillary pressures of over 100 mm. Hg if the deficit is to be explained solely on the basis of filtering out.

The anomalous behavior of these metabolically inert substances is not peculiar to the eye. Similar deficits of the same or similar substances have been found in the spinal fluid. The classical study of Amberson and Höber[2] on the salivary gland revealed that the transfer into the saliva of substances of this type is retarded increasingly as their molecular size increases. If, however, these substances are compared with their chemical derivatives of increasing lipoid solubility, the discrepancies tend to disappear. No satisfactory general theory has as yet been presented to explain the anomalous behavior of the group of substances of which urea may be taken as the prototype, but some conclusions are obvious.

The deficit of these substances in the aqueous and in various other body fluids cannot be accounted for *solely* by physicochemical processes of diffusion and ultrafiltration. Some contribution of cellular or tissue metabolic energy is required to account for the deficit, some sort of secretory phenomenon is involved. Either these substances are secreted out, that is, actively excluded by the blood-aqueous boundary—and this seems wholly unlikely in view of their metabolic inertness—or something else, that is, water or electrolytes or both, are secreted in.

In the latter case, the osmotic retardation of water movement would be overcome by the active secretory mechanism and the relative retardation of urea and other similarly acting substances *could* be attributed to a filtering process.

These conclusions have been greatly fortified by the work of Kinsey and Grant who studied not merely the equilibrium ratios between plasma and aqueous for urea and a variety of electrolytes, but their rates of transfer from plasma to aqueous and from aqueous to plasma. The mathematical formulation of the monumental mass of data which they obtained is necessarily complex, and the particular analysis used by Kinsey and Grant has been criticized by Duke-Elder and Davson.[14] I shall not burden the argument with a discussion of the various possible alternative mathematical equations.

What can be concluded from Kinsey and Grant's data[26] is: (1) The data are not compatible with an hypothesis of simple diffusional exchange with or without ultrafiltration into the eye, and ultrafiltration or leak out of the eye; (2) the data are compatible with the combination of the following hypotheses: (a) Electrolytes are transported into the eye by a secretory process, (b) in the presence of such electrolyte secretion, the retardation of urea can be accounted for by ultrafiltration; (3) the data demonstrate that reabsorption of the intraocular fluid occurs at least in part in the fashion of a leak, that is, by a mass transfer out of the eye of fluid with all its solutes undisturbed in the reabsorption process by diffusional exchange.

No doubt some other more complicated sets of hypotheses would also fit the data. However, until new data indicate that more complicated hypotheses are required, these studies of Kinsey and Grant add strong support to the conclusions outlined above from a consideration of the equilibrium levels of electrolytes and of urea, and, in addition, throw new and important light on how the reabsorptive mechanism may be conceived as operating.

Returning now to glucose, it would appear that this substance is somewhat out of line with the group of lipoid insoluble, water soluble, nonelectrolytes. If account is taken of intraocular consumption of glucose, the transfer of this substance may not be retarded at all. We have here, then, a possible suggestion that glucose is actively secreted into the eye. The exceptional position of glucose and of other metabolized sugars is, again, not unique for the eye. A large literature exists indicating an active transport of various metabolized sugars across the intestinal wall. It is thought that an active metabolic process by which these sugars are phosphorylated at one side of the boundary, and de-phosphorylated at the other side may explain their active transfer. There is, however, no necessary implication that this active transport of metabolized sugars is associated with an over-all movement of water. According to a currently held theory, glucose is present in the glomerular filtrate in the kidney by simple diffusion without any active secretion involved. It is reabsorbed by the tubules by an active secretory mechanism. Intravenous injections of glucose produce a marked diuresis. Therefore, the increase in the active transfer of glucose from the tubules back to the blood stream is not accompanied by a corresponding increase in tubular reabsorption of water.

Ascorbic acid is present in the aqueous of many mammals, including man, in concentrations very markedly higher than in the plasma. In rabbits the concentration ratio is about 10 to 1. The excess of ascorbic acid in the aqueous might be the result of local synthesis or of active transfer. Both these possible explanations have been advanced with some experimental support. Local synthesis, however, seems very unlikely because guinea pigs, monkeys, and man all show an excess of ascorbic acid in their aqueous, although animals of these species are unable to synthesize ascorbic acid and suffer from scurvy if vitamin C is eliminated from their diet. In fact, the disappearance of ascorbic acid from the aqueous is a very early symptom of

vitamin-C deprivation in guinea pigs, and this could not be true if it were being synthesized locally independent of the supply in the plasma.

Goldmann and Buschke[30-32] showed that over a wide range of concentrations, the aqueous ascorbic-acid level fluctuates in proportion to the plasma level. They concluded that the aqueous ascorbic acid was derived from that in the plasma, and that the excess concentration in the aqueous must be attributed to active transport rather than to local synthesis. Kinsey[36] has carried the argument still further. If ascorbic acid is actively transferred into the aqueous, then there must be some limit to the capacity of the transferring mechanism. Within the physiologic range he confirmed the findings of Goldmann and Buschke, but when the plasma ascorbic-acid level was pushed very far above the normal range, an upper limit of aqueous ascorbic-acid concentration was reached.

There seems no doubt, then, that ascorbic acid is actively transferred into the aqueous. Here also the ocular tissues are not unique. The concentration of ascorbic acid in the saliva, the tears, and in many other secretions is higher than that in the plasma. There is however, no reason to assume in advance that the active transfer of ascorbic acid across these various tissue boundaries is linked with an active transfer of water. The two mechanisms, even when simultaneously present in the same organ, might in fact be wholly independent.

Finally, we come to hyaluronic acid, the mucoid component of the vitreous, which, as Karl Meyer[41] has shown, is present in appreciable concentration in the aqueous and not measurably present in the blood plasma. If aqueous is withdrawn from an eye, it is rapidly replaced by plasmoid aqueous in which the hyaluronic acid content is low, but from this low level the normal concentration is slowly reattained. If excess hyaluronic acid is injected into the anterior chamber, the excess, at first rapidly and then more slowly, disappears. One must conclude that

hyaluronic acid is normally secreted into the ocular cavity, and, since this substance is not present in the plasma, we must be dealing here with local synthesis rather than active transfer.

Again we must ask, and leave for the present unanswered, the question whether the local synthesis of mucoid is in any way linked with fluid transport. There are many tissues in the body in which mucoid synthesis occurs without any obvious relation to fluid transport, for instance, the umbilical cord, the synovial tissues, cartilage, and so forth. There are also some organs, for instance, serous glands, the kidney, and liver, in which fluid transport occurs without mucoid synthesis. There are, however, many mucous glands in which mucoid synthesis and fluid transport are conjoined, and in which the two processes may nor may not be integrally linked.

The conclusions which seem to me justified from studies on the chemical composition of the aqueous may be summarized as follows: (1) Hyaluronic acid is secreted into the ocular fluid in the sense that it is synthesized locally. (2) Ascorbic acid, certainly, and glucose, possibly, are secreted into the intraocular fluids in the sense of active transfer from plasma to aqueous. (3) The osmotic measurements of Duke-Elder and Davson and the transport measurements of Kinsey and Grant are compatible with the notion that electrolytes are actively secreted into the ocular fluid, that water follows by osmosis, that urea and like substances are filtered out in the process, and that the reabsorption of the intraocular fluid is by a process equivalent to leakage.[16, 17]

If this seems unduly complex, I cannot apologize, for the state of the subject is complex. Rather I must apologize for making these studies seem unduly simple. Accurate chemical measurements on substances present in low concentration, in the minute volumes of fluid that can be obtained for analysis, present major problems in chemical technique for their solution. It is no wonder that the results of different investigators are

occasionally conflicting. Rather it is a great wonder and a great tribute to the meticulous care and diligent labor of this group of investigators that their results have achieved broad and substantial agreement. Also, it is no wonder that debate regarding the interpretation of the results has been lively, for the subject has intrinsic importance, and the persons concerned are lively.

Having reached thus far it seems appropriate to ask: if there are secretory contributions to the intraocular fluid, where do these several secretory acts take place, what are the mechanisms involved in these several secretory processes, are these mechanisms independent or integrally linked with one another, how are these mechanisms activated and how controlled? These questions form the logical background of those studies that I have been asked to summarize. I hasten to add that these questions were not, historically, the background of the studies that I undertook in this field, for information as to the chemical composition of the aqueous was at that time much less well defined than it is now. The most that I asked myself at that time was: Supposing there is secretion of the intraocular fluid, where and how does this take place?

A clue as to "where" came to us early from studies on the reabsorptive mechanism.[16] If the eye is connected with a fluid reservoir and the pressure raised far above normal, fluid runs into the eye from the reservoir at a steady rate, and is absorbed from or escapes out of the ocular cavity at a corresponding rate. It was easy to show that the escape or absorption occurs almost exclusively from the anterior chamber, that the tissues behind the iris do not participate appreciably in the absorption or provide the portal of escape.

If the ocular tissues are poisoned by cyanide, on the other hand, quite appreciable quantities of fluid are absorbed by tissues behind the iris at supranormal intraocular pressure. It was evident that some metabolic processes were involved in the resistance which the posterior ocular tissues offer to the absorption of fluid. When the intraocular pressure is brought below its normal level, the anterior chamber becomes shallow, and fluid enters the posterior chamber at a considerable rate. Under these circumstances, the fluid in the posterior chamber and in the Greef vesicles that form on the ciliary processes becomes plasmoid.

It is plain, then, that some tissue behind the iris exhibits in its unpoisoned state the phenomenon of irreciprocal permeability to water. Phenomena of this type have been widely found associated with secretory organs. We concluded that if there was an organ for the secretion of the intraocular fluid, it was probably located behind the iris, and since nothing pointed to the retina as a possible secretory organ, we concentrated our attentions on the ciliary body.

The supposition that the ciliary body might be an organ of secretion was strongly supported by our experience with the variety of dyes.[18] This tissue shows a remarkable and coherent set of phenomena of anomalous transport with respect to a large number of crystalloid dyes, tending to accumulate basic, that is, cationic dyes, in the epithelium and acid, that is, anionic dyes in the stroma. The final distribution of the dye is the same irrespective of whether it is introduced to the tissue on the epithelial side or into the stroma via the blood stream.

Phenomena of this type are always subject to the possible suspicion that they represent the result of selective staining rather than anomalous transport. We were very fortunate, therefore, to find that these phenomena could be studied in the excised tissue maintained supravitally. If the tissue was poisoned with cyanide, the anomalous behavior of the dyes disappeared. If the tissue was placed under nitrogen, the anomalous behavior of the dyes disappeared reversibly, and reappeared on readmission of oxygen. Such behavior could not possibly be attributed to selective staining.

It was concluded, therefore, that the anom-

alous distribution of these dyes in the ciliary processes represented a true example of anomalous transport, and that the anomalous transport was dependent upon the oxidative metabolism of the tissue. We concluded further that, if there was secretion of the intraocular fluid, the ciliary processes were a likely site of the secretory mechanism for here was a tissue that exhibited a veritable exuberance in pushing things around.

Having decided to search in the ciliary body for a possible secretory mechanism it was necessary first to clarify our own ideas as to what we were looking for. By a secretory mechanism concerned in water transport, we mean an arrangement of elements in the tissues, such that the chemical energy of cellular metabolism is converted into mechanical energy of water movements.

Let us consider this problem from the point of view of an engineer, and ask ourselves how the chemical energy of metabolism could conceivably be converted into the work of water movement. The chemical energy of metabolism becomes available primarily through the interaction of substrates with enzymes or enzyme systems. Insofar as the enzymes and substrates are considered as being suspended or dissolved in a fluid environment, no effective conversion of chemical energy to water transport appears possible, for the mechanical transport of water requires at least some sort of boundary across which the water is to be transported, such that the water, once moved through the boundary, will not immediately flow back to its original position. The first requirement for a water-secreting system, then, is a boundary across which the secretory work is to be performed.

Given such a boundary, the second requirement is that the metabolic processes on the two sides must differ from each other so as to generate a difference in the potential energy on the two sides of the boundary. Only when there is a difference in potential energy between two parts of a system is there free energy available to do mechanical

work. The difference in potential energy on the two sides of the boundary might exhibit itself in osmotic or electrical or other form.

It follows that the third requirement for a water-secreting mechanism is that the characteristics of the boundary must be such as to transform the free energy into the work of water movement. The particular characteristics required of the boundary depend on the form in which the energy is available, but, in any case, both a difference in potential energy across a boundary and a boundary whose special characteristics are appropriately related to the special form of available energy are required.

The significance of these basic requirements will become clearer if I digress briefly to indicate the present status of theories regarding water transport in the domain of general physiology. Work in this field has been enormous in its extent, and has engaged some of the best minds of our generation. Any brief compendium that I can make will necessarily present only a simplified and inadequate picture. Even the large monographs by Gellhorn,[29] Höber,[32] and Davson and Danielli[9] present each a truncated account of the matter. Nevertheless, the problem of ocular-fluid transport cannot be viewed in isolation but only against the background of knowledge and thought regarding fluid and solute transport in the domain of general physiology. The problems of ocular-fluid transport constitute but one small item in this general field. It may be stated at the outset that no satisfactory general theory of water secretion has so far been developed, largely, it seems to me, through neglect of consideration of the basic engineering requirements outlined above. Nevertheless, a vast number of careful and interesting observations have been made.

In serous glands the epithelial cells contain many cytoplasmic granules. Observations in vivo have revealed that during secretion certain of these granules, the so-called zymogen granules, grow rapidly in size and are discharged into the lumen. It is not clear

whether the contents discharged into the lumen are chiefly solid matter which is diluted and dispersed in the watery secretion provided by some other mechanism, or whether the swollen zymogen granules are in essence vacuoles, similar to the excretory vacuoles of the protozoa. In the latter case, the boundary of the vacuole would be that across which the secretory transport actually takes place. Even in the former case, the introduction into the lumen of water-soluble colloidal material could, through its colloid osmotic pressure, play a role in water transport.

In mucous glands the mucoid material can clearly be seen in a sharply outlined region in each goblet cell. Presumably the interior of the goblet contains enzymes capable of synthesizing the mucoid while the boundary is presumably permeable to the substrates out of which the mucoid is synthesized, but impermeable to the synthetic product. Mucoids are hydrophilic colloids and their synthesis must be accompanied by an accumulation of water in the goblet, and this water along with the mucoid is eventually discharged into the lumen. Since the molecular size of the mucoids is enormous, their colloid osmotic pressure is not very great, and the amount of water transported in this fashion is probably relatively small.

Some indication of the probable magnitude of the mucoid contribution to water transport may be reached in respect to the eye. The protein osmotic pressure of plasma, that is, the hydrostatic pressure at which plasma is in equilibrium with its dialysate is generally estimated at about 25 mm. Hg. This is the osmotic pressure of a 1.5 millimolar solution of a nonelectrolyte. Plasma contains about 6 percent of proteins or 60,000 mg. per liter. From these two figures one can estimate that the average molecular weight of the plasma proteins should be about 40,000, a figures which agrees well with more direct determinations.

According to Meyer, the vitreous contains 2.5 percent of mucoid. In order that the colloid osmotic pressure of the vitreous should equal that of the blood, the average molecular weight of the mucoid molecules would have to be about 1,500. The estimated molecular weight of hyaluronic acid is of the order of 100,000, consequently the synthesis of mucoid can contribute only a very small factor of water transport into the eye. As a matter of fact, if the colloid osmotic pressure of the vitreous mucoid were appreciable, there would necessarily be a corresponding excess of hydrostatic pressure in the vitreous as compared with the aqueous, since the latter contains only one sixth as much mucoid as the former.

Actually the difference in pressure, if any, is very small. While the aqueous cannot, therefore, be accounted for as a mucous secretion, this analysis reveals the role of a difference in potential energy, in this case colloid osmotic plus hydrostatic pressure, operating across a boundary, in this case a simple semipermeable membrane. In the synovial cavities, in which the mucoid concentration is very high, a mechanism of the type outlined might account for the whole of the water content.

The frog's skin has been the subject of extensive studies. When this tissue is placed as a diaphragm between two chambers of isotonic salt solution, fluid is transferred from the epithelial to the subcutaneous side. The transfer is inhibited by cyanide. An electric potential difference is measurable across the membrane and this is also suppressed by cyanide. Much has been made of the fact that under these postmortal conditions the corium tends to swell more actively than the epithelium, but there is no reason why such a local swelling should effect a net transfer of fluid.

It is, nevertheless, possible to conceive of a system in which reversible turgescence could play a role in water transfer. If the boundary material became alternatively hydrophilic and hydrophobic on reversible chemical change, for instance, if it became hydrophilic on oxidation and hydrophobic on reduction, and if the respiratory metabolism

of the tissues on the two sides was such that one tissue tended to oxidize the boundary, the other to reduce it, then water would be added to the boundary on the oxidizing side and removed from it on the reducing side, the boundary constituting at the same time a link in a hydrogen transport chain between a set of oxidases in one tissue, and reductases in the other.

Reversible oxidation and reduction is not the only chemical change that can be conceived of as related to reversible hydration and dehydration. Esterification and de-esterification might have a similar effect. Changes in pH are also notorious in their influence on water binding. A system in which such opposite chemical changes were continuously occurring on opposite sides of the boundary would transfer water toward the dehydrating side while at the same time transferring the reacting group in the same or in the opposite direction.

Another interesting field of physiologic study in this connection is that of the fresh-water fish. These animals maintain an internal environment hypertonic in electrolytes to their external environment. Water enters by osmosis through the gills which are presumably relatively impermeable to electrolytes, and the excess water is excreted by these animals in the form of very hypotonic urine This accounts for the homeostasis of the fish, although the renal mechanism is not understood, but leaves out of account the fact that some electrolytes have to be accumulated during growth, and also to make good the small renal losses. No mechanism for such accumulation has been proposed. If the fish get their inorganic salts from their food, the problem of salt accumulation is merely displaced to another species.

The process of electrolyte accumulation is again the key problem in respect to the movement of water in the sap of plants. The concentration of electrolytes, particularly of potassium salts, in the sap is much higher than in the soil water in which plants' roots are exposed. Thus water is drawn into the roots by osmotic forces and is lost from the leaves by evaporation. Consequently the water transport in plants presents no critical problems except in those special species whose leaves "sweat." But as the plant grows it increases its electrolyte content by accumulation out of a hypotonic environment. A possible explanation of this accumulation is available in the supposition that metabolic activity in plant cells produces organic acids which are either nondiffusible or unable to permeate through the cell wall. If the cell wall is, then, permeable to hydrogen ions and potassium ions, an exchange could occur leading to an accumulation of potassium within the cell. This hypothesis, however, requires that the pH of the cell should be below that of the soil, a requirement that does not appear to be generally fulfilled. We are left, therefore, with the need to explain an active transport of potassium ions.

Similar problems of accumulation confront the mammalian physiologist. While the total concentration of electrolytes inside and outside of the body cells is approximately equal, most cells (perhaps not all) contain potassium as their chief inorganic cation, while the body fluids contain chiefly sodium. In the red blood cell the ratio of potassium to sodium is 10 to 1, while in the plasma it is 1 to 50.

An easy explanation in the past has been that the red-cell membrane is impermeable to cations and, having been loaded with its quota of potassium, it holds this quota throughout its life by simple inert non-exchange with the adverse environment. This hypothesis, of course, fails to explain how the potassium got inside the red cell in the first place.

Recent studies with radioactive sodium, however, have shown that the red-cell membrane is not completely impermeable to sodium. If red cells are suspended in plasma containing radioactive sodium, either in vivo or in vitro, an exchange of normal sodium for radioactive sodium takes place, so that the small amount of sodium inside the cell,

only 10 percent of its total inorganic base, eventually contains the same fraction of radioactive isotope as is present in the plasma. According to Cohn and Cohn,[5] 50 percent of the equilibrium ratio is reached in 8 hours. These new experiments taken at their face value indicate that the theory that cell membranes are impermeable to cations does not suffice to explain the maintenance of the high intracellular K :Na ratio, just as it fails to explain the anomalous accumulation of potassium in the cell during growth.

The problems of renal physiology are even more complicated for here the glomerular filtrate which is in effect a dialysate or ultrafiltrate of the plasma, passes successively through at least 4 different tubular organs which transfer a variety of substances into and out of the urine. Although there is considerable knowledge of the net exchange, very little is as yet known about what substances are transported conjointly in a single functional segment of the renal tubule.

It is to be admitted in frank veneration of the enormous achievements of the general physiologists in these various fields, that the problems of water transport and of ionic transport are extremely difficult and complex, and that this complexity is still further compounded in many of the organs that have, for various reasons, engaged their special interest. Thus the kidney is not a single secretory organ but a whole group of such organs arranged in series.

The serous glands present not merely special problems in the special composition of their secretory product, but are further complicated by special start and stop mechanism involving neural or humoral controls. Study of the mucous glands is handicapped by lack of knowledge of the biochemical mechanisms of mucoid synthesis. The problem of salt accumulation in plants is inextricably linked with the still more recondite problem of growth.

It is the fortunate privilege of ophthalmologists that we have been forced to devote our attentions to a potential secretory organ in which the secretory product differs little from a dialysate of the plasma, in which special synthetic metabolic processes appear to play only a minor or indirect role, in which the special complexities of start and stop mechanisms appear not to be present, in which the perplexing problems of growth need not be held in the forefront of our minds. The chorioid plexus is, perhaps, an equally happy choice for introductory studies in this problem, but other comparably suitable test objects are few or at any rate hard to find.

Returning, then, to the ciliary body, we have as a firm beginning for our study the anomalous transport of anionic and cationic dyes. The boundary across which this transport operates is the boundary between stroma and epithelium. There is, at this point in the study, no reason to believe that water is also transported across this boundary, but we can at any rate attempt to disentangle the mechanism of dye transport, and see where this will lead us.

The argument set out above requires that we seek the source of energy for the dye transport in terms of a difference in potential energy on the two sides of the secretory boundary. Since the anomalous transport of dyes disappears reversibly under asphyxia, it is clear that the energy that we seek to identify is ultimately derived from the oxidative metabolism of the tissue. Such energy might become available to the secretory boundary in a variety of forms. There might be a difference in the redox potential on the two sides of the boundary. There might be a difference in the availability of substances with high energy phosphate bonds, or of some other reactive substances on the two sides of the boundary.

We chose initially to explore the first of these possibilities for several reasons. In the first place, there was available, particularly from the work of Clark and Cohen,[6] a series of indicator dyes with the aid of which intra-

cellular redox potentials could be estimated. In the second place, there was, in respect to the potential intraocular secretory mechanism, some a priori doubt as to whether a coherent theory of secretion on the basis of phosphate bond energy could be worked out.

In a secretory mechanism which derives its energy from high energy phosphate carriers, the boundary would, in accordance with the principles outlined above, be continuously phosphorylated on one side and de-phosphorylated on the other, the dephosphorylation yielding the energy for the secretory transfer. This possible arrangement, however, would, of course, include an active transfer of phosphate across the boundary. A secretory organ that operated in this fashion should yield a secretion that was either very rich or very poor in phosphate unless there were associated with it some additional device for phosphate equilibration. Since the inorganic phosphate of the aqueous does not differ considerably from that of a plasma dialysate, explorations of this possibility appeared at best a second choice.

Experiments with redox indicator dyes,[18] introduced into the ciliary tissues without mechanical trauma, revealed that these tissues possessed well-poised potentials. The results with a large series of dyes of very varied chemical structure gave a consistent pattern, and one which was altered consistently by altered experimental conditions such as anoxia and cyanide poisoning. The interpretation of these results requires, however, great caution. The fundamental considerations involved in such interpretation have been indicated in the classical studies of Cohen and Chambers[5,7] on the intracellular redox potential of protozoa.

Redox indicator dyes are chemical substances which are readily and reversibly oxidized and reduced, and which change color on oxidation and reduction. They change from their reduced to oxidized state or vice versa in a characteristic fashion depending on the redox potential of the environment in which they are placed, and with which they react. The redox potential at which an equal mixture of the oxidant and reductant of the indictor is present, that is, the midpoint of their color change, is characteristic for each indicator, and varies with pH.

The first requirement for the valid use of such indicators, therefore, is that the pH of the environment in which they are reacting should be known. In the ciliary body we used pH-indicator dyes, and tested the reliability of these pH indicators in the tissue by immersing the tissue with its indicator dyes in buffer solutions of known pH, and found that under these circumstances the pH-indicator dyes assumed the expected colors characteristic of the pH of the buffer solutions. There was, therefore, nothing in the tissue that violently disturbed the reliability of the pH indicators.

Using these indicators, then, without surrounding buffers we found that the pH of the tissue studied supravitally was in the reasonably expected range, close to pH 7.4. This was, then, the pH at which the redox potential was to be estimated.

The characteristic potential of each of the redox-indicator dyes in simple aqueous solution is well known. In the complex protein-laden internal environment of the cell, the thermodynamic activity of the indicator molecular special may not be the same as in the simple in vitro solutions, and errors may thus be introduced into the estimate of intracellular redox potential.

A similar problem, of course, arose in respect to the use of pH indicators for the determination of intracellular pH. It was for this reason that the experiments were made of immersing tissue with indicator-pH dyes in buffered solution. The fact that no significant difference in color was observed between the dyes in the tissue and in the surrounding buffer solution indicated that the difference in activity of the indicator within

the cell from that outside in the buffer solution was negligible within the range of accuracy of the measurement, in this case amounting to one to two tenths of a pH unit.

Similar variations in thermodynamic activity of the redox-indicator dyes would not introduce errors in the estimate of intracellular redox potential of more than ±10 millivolts. The observational error of the experiment itself left an uncertainty of ±15 millivolts. The substantial concordance of results with a whole series of dyes of very varying chemical configuration further supported the conclusion that errors in the estimate of intracellular redox potential due to unknown variation in thermodynamic activity of the indicators within the tissue were small. In any case the total uncertainty of the redox potential measurements would be smaller than ±30 millivolts, and would be small compared to the differences actually found in the different tissue regions.

A third consideration in the interpretation of these observations is somewhat more complicated. When oxidants and reductants are mixed in a test tube, they interact until they reach an equilibrium composition. If a small amount of indicator dye is introduced into the mixture, it reacts with the components and comes to equilibrium with them. The resulting color of the indicator is used to estimate the redox potential of the system. Within cells and tissues no such equilibrium exists. At most we can deal only with steady states. Some enzymes in the cells are continuously reacting with molecular oxygen and becoming oxidized in the process. The oxidized enzymes in turn react with other cellular components oxidizing these components, and themselves becoming reduced and capable of again reacting with molecular oxygen. The cellular components which have been oxidized in turn oxidize other components, and this chain of reactions continues by successive links until finally metabolites are reached. This chain of reactions has many links. Some of the links are proteins,

that is, enzymes. Other links are diffusible substances which carry the oxidation and reduction from one enzyme to another. Some of these diffusible links in the chain are independently reactive while others are sluggish in their reactions except when activated by association with the appropriate enzymes.

The independently reactive substances within the cell thus constitute a pool which will tend to be more oxidized or more reduced depending on the bottle necks in the reacting chain. If oxygen is not available or if the enzymes that normally react with oxygen are poisoned, for instance with cyanide, the level of oxidation in the pool will fall. If oxidizable metabolites are not available, or if the enzymes that normally catalyze their oxidation are poisoned, the level of oxidation in the pool will rise. In two tissues both of which have adequate supplies of oxygen and of metabolites, the oxidative levels in the pools will depend on the abundance and enzymatic activities of the various enzyme systems within them.

When redox-indicator dyes are introduced into cells, they react with and become a part of the intracellular pools of reactive substances. The redox potential determined by the indicator is that of the pool of substances with which they react. The existence of well-poised potentials within cells observable by this means does not at all imply that all the substances within the cell are in equilibrium with this potential. Nevertheless, the recorded potentials do in fact indicate the balance within the cells between oxidative and reductive processes. In the ciliary body, the measurements with indicator dyes showed that there was a difference in apparent redox potential between the epithelium and the stroma of almost one quarter of a volt, the epithelium being the more oxidizing tissue.

Such a difference between these two tissues might be due, as indicated above, to a difference in the enzymatic constitution of the two tissues. This proved to be the case. In a series of studies[22, 25, 27] in which the

epithelium and stroma of the ciliary body were mechanically separated from one another, and then analyzed separately for their enzyme content, it was found that the epithelium contained an abundant supply both of enzymes that react with molecular oxygen (the cytochrome oxidase system), and of enzymes that catalyze the oxidation of carbohydrate substrates (for example, lactic and malic dehydrogenases). The ciliary stroma, on the other hand, contained no detectable enzymes that react directly with molecular oxygen, but nevertheless contained an abundant supply of lactic and malic dehydrogenases, roughly as much per cell as in the epithelium.

The existence of adjacent tissues operating under different respiratory patterns has long been known. Like so many other aspects of modern cellular physiology, the existence of such phenomena was first described by Ehrlich,[15] who spoke of oxidative sources and sinks in the tissue. Adjacent tissues supplied with differing respiratory enzyme systems may presumably coexist without any mutual metabolic relations, or they may exchange metabolites or some other components in a sort of symbiosis. Finally they might conceivably interact directly if the boundary between them were itself reversibly oxidizable and reducible. It is this latter form of direct interaction which, if present, might, under appropriate conditions, serve as the mechanism of secretory transport. Before inquiring into the appropriate conditions required for secretory transport, we must first decide whether the boundary in the ciliary body is reversibly oxidizable.

So far as the anomalous transport of anionic and cationic dyes is concerned, the boundary lies at or near the junction of epithelium and stroma, and coincides in effect with the boundary of differing redox potential. Unfortunately, we have found no way in which this boundary can be mechanically isolated and subjected to direct chemical study. It is quite possible, in fact, that the effective boundary may be merely a mono-molecular layer. Consequently, it was difficult to plan an experimental approach by which the chemical characteristics of the boundary could in part be revealed. We were very lucky to find that, under conditions under which the active anomalous transport of dyes was suppressed, that is, under asphyxia or cyanide poisoning, the boundary exhibits a selective permeability, being more permeable to anionic than to cationic dyes. Moreover, this selective permeability was reversed at lower pH.

We were thus provided with a means by which the isoelectric point of the boundary could be determined, and found that the isoelectric point could be shifted reversibly on exposing the tissue to oxidizing or reducing solutions. Moreover, the level of oxidizing potential required to shift the isoelectric point partially toward its value in the oxidized state was not greater than that normally present in the epithelium under aerobic conditions, and the level of reducing potential required to shift the isoelectric point back to its value on reduction was no greater than that normally present in the stroma. The boundary, therefore, has the characteristics required to serve as a link between the redox-reactive pools of materials in the epithelium and in the stroma.

On oxidation the isoelectric point of the boundary shifts toward higher pH, and the isoelectric zone becomes broadened, indicating that strong basic groups appear on oxidation. However, even on oxidation the isoelectric point remains on the acid side of physiologic pH, consequently the overall charge on the boundary is negative in both its oxidized and its reduced states. There are many familiar substances in which strong basic groups appear on oxidation. Methylene blue is such a substance. Nicotinamide which furnishes the redox groups in coenzyme I and II has similar properties.

When any substance is oxidized, the primary reaction consists in the loss of one or more electrons. It is for this reason that characteristic electrical potentials are found

in relation to redox reactions. The electron loss may be associated with the loss of a hydrogen ion. In this case the overall effect of oxidation is the removal of hydrogen from the substance oxidized. Or again, the loss of electrons may be associated with the uptake of water and loss of hydrogen ions. In this case the overall effect of oxidation is the addition of oxygen to the substance oxidized. In either of the latter cases no net change in electrical charge need occur in the substance oxidized.

A boundary composed of a substance of one of these sorts, operating between two systems of differing redox potential, would transfer a hydrogen ion from the reducing side to the oxidizing side with each electron. Electrical neutrality would thus be maintained at each step of the reaction, and nothing else need be transported in the process. Such systems would not in general act as secretory mechanisms. Incidentally a boundary composed of such substances would suffer no change in its charge, and hence no appreciable shift in its isoelectric point on oxidation and reduction.
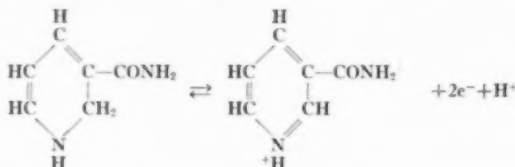
For almost all such substances there exist pH ranges in which the electrically compensating loss of hydrogen ions is incomplete or absent. In such case the oxidized substance suffers a net loss of anionic charges or a net gain of cationic charges. Compare, for instance, the oxidation of hydroquinone at low pH:

$$\text{hydroquinone (HO–C}_6\text{H}_4\text{–OH)} \rightleftharpoons \text{quinone (O=C}_6\text{H}_4\text{=O)} + 2e^- + 2H^+$$

with the same reaction at high pH:

$$\text{(}^-\text{O–C}_6\text{H}_4\text{–O}^-\text{)} \rightleftharpoons \text{(O=C}_6\text{H}_4\text{=O)} + 2e^-$$

or the oxidation of nicotinamide at low pH:

$$\text{dihydronicotinamide (N}^+\text{H}_2\text{, –CONH}_2\text{, CH}_2\text{)} \rightleftharpoons \text{nicotinamide (N}^+\text{H, –CONH}_2\text{, CH)} + 2e^- + 2H^+$$

with the same reaction at high pH:

$$\text{(NH, –CONH}_2\text{, CH}_2\text{)} \rightleftharpoons \text{(N}^+\text{H, –CONH}_2\text{, CH)} + 2e^- + H^+$$

There are indeed very many substances in which the electrically compensating loss of hydrogen ions is absent or incomplete on oxidation at physiologic pH. A boundary composed of one of these latter substances, operating between two regions of differing redox potential, would not transfer a hydrogen ion from the reducing side to the oxidizing side with each electron. The maintenance of electrical neutrality in such cases could be accomplished only through a net transfer of cations from the reducing to the oxidizing side, or of anions in the opposite direction or both. Such a transfer of ions is precisely that which we have found to characterize the anomalous transport of anionic and cationic dyes in the ciliary body. Moreover, a boundary of this type would suffer a net change in its electrical charge, and con-

sequently a shift of its isoelectric point with oxidation and reduction. It is to be concluded, therefore, that an oxidative interaction of the type described would satisfactorily account for the phenomena of anomalous dye transport in the ciliary body.

The full course of one cycle of oxidative interchange between the two tissue components can be outlined as follows: The ciliary epithelium contains cytochrome oxidase, and the anomalous dye transport is inhibited by cyanide. We can assume, therefore, that the oxidative cycle begins with the oxidation of cytochrome oxidase by molecular oxygen, a process which requires the transfer of electrons from the cytochrome oxidase to oxygen.

(1) Reduced cytochrome oxidase $+ \frac{1}{2}O_2 \rightarrow$ oxidized cytochrome oxidase $+O^-$

(2) $O^- + H_2O \rightarrow 2\overline{OH}$

In a system buffered by bicarbonate there would follow:

(3) $$2\overline{OH} + 2CO_2 \rightarrow 2H\overline{CO_3}$$

Regeneration of reduced from oxidized cytochrome oxidase we assume occurs in respect to the particular chain of events that we are following, at the expense of corresponding oxidation in the boundary. When this latter has been reduced by the stroma, the net effect of the reduction of one atom of oxygen so far as the epithelium is concerned is to produce in the epithelium two new anions (bicarbonate ions) not completely balanced locally by corresponding cations.

The reduction of the boundary by the stroma occurs ultimately at the expense of oxidation of a metabolite.

(4) $$RH_2 - 2e^- \rightleftharpoons R + 2H^+$$

Again, in the presence of bicarbonate buffer

(5) $2H^+ + 2Na^+ + 2H\overline{CO_3} \rightleftharpoons 2Na^+ + 2H_2O + 2CO_2$

Thus the full effect of one cycle involving the reduction of one atom of oxygen in the epithelium, and the oxidation of one molecule of metabolite in the stroma, yields a net gain of two incompletely balanced anions in the epithelium and two incompletely balanced cations in the stroma. Electrical neutrality under these circumstances can be maintained only by a transfer of anions from epithelium to stroma, or of cations from stroma to epithelium. Such an ionic transfer constitutes an ionic electrical current, balancing and neutralizing the electronic transfer of the redox interaction. Which of the two phases of the ionic current will predominate, that is whether the ionic current will consist predominantly in a transfer of anions toward the stroma or of cations toward the epithelium will depend on the character of the boundary.

We have already seen that the boundary in its reduced state is isoelectric at pH 5.5. It is, therefore, an amphoteric substance containing both acidic and basic groups, the dissociation constants of which are such that at physiologic pH, the number of dissociated acid groups exceeds that of the dissociated basic groups yielding a net overall negative charge on the boundary relative to the surrounding watery medium. Elementary considerations of electrostatic forces lead to the conclusion that in the layer of fluid immediately adjacent to such a negatively charged boundary, the so-called adsorbed layer, there would be a relative excess of cations and deficit of anions as compared with the surrounding fluid.

On oxidation of the boundary, some new basic groups appear in it and the isoelectric point is shifted to pH 6.5. At physiologic pH there is, therefore, even in the oxidized boundary a net excess of dissociated acid groups, and a net overall negative electrical charge on the boundary relative to the surrounding medium. Under these circumstances there would still be a relative excess of cations and deficit of anions in the adsorbed layer compared with the surrounding fluid, although the excess of cations and deficit of anions would be less marked than

when the boundary is in its reduced state.

Bethe and Toropoff[4] have shown that the imposition of an ionic electrical current across a charged membrane in a saline environment leads to the predominant movement of those ions that are present in excess in the adsorbed layer. The application of their findings to our case would lead to the conclusion that the predominant ionic movement in the maintenance of overall electrical neutrality would be that of cations (sodium ions) from the stroma to the epithelium. Osmotic and electro-osmotic movement of water would, of course, accompany the cations. The net product of such a secretory organ as we have so far identified in the ciliary body would be a slightly hypertonic fluid whose chief electrolyte constitutent would be sodium bicarbonate. Since this does not correspond to the facts, it is evident that the analysis given so far cannot be complete.

The pattern of organization pictured so far, although incomplete, is not absurd. There are several secretory organs which do, in fact, produce a secretion consisting chiefly of a slightly hypertonic solution of sodium bicarbonate. The salivary secretion of the cud-chewing herbivora is an example of such a secretion. The coelomic fluid of the turtle has been shown by Homer Smith to contain chiefly sodium bicarbonate. The basic reaction of the secretion of the small intestine is in man no doubt the result of the predominance of bicarbonate among its anions.

In the intraocular fluid the chloride-bicarbonate ratio is approximately the same as that in the plasma. If the primary secretion product is bicarbonate solution, the conversion of this to the composition of the actual aqueous could occur as the result of an ionic exchange. Exchanges of this type are well known in many biologic processes and can be extremely rapid.

A phenomenon closely related to that which is here postulated has been extensively studied in the blood. On passing through the peripheral capillaries the red blood cell loses oxygen, some acidic groups of the hemo-globin become undissociated, and bicarbonate ions are picked up. In passing through the pulmonary capillaries the reverse process takes place. Each capillary transit requires, on the average, only a few seconds at most, and yet equilibration is effectively completed each time. No special mechanism appears to be required to account for such an exchange as is here postulated. Rather we must wonder what special mechanism impedes such an exchange in organs like the small intestine.

I have given an account of the studies into which we were led, and of the argument that we have followed in search for an explanation of the anomalous dye transport in the ciliary body. These studies have revealed a complicated arrangement of complicated substances in the tissue, some of which we have identified approximately as to their nature and their location.

If chemical reactions between these substances do, in fact, occur in accordance with the general organized pattern in which we have shown they might occur, then the anomalous dye transport would be fully accounted for and, in addition, there would be a secretory transport of electrolytes and water from stroma to epithelium.

Up to this point in the argument, evidence is lacking as to whether the tissue components do in fact interact in the way we have shown that they might interact. Even if we assume that such interaction does in fact take place, we have no quantitative measure of how much of such interaction takes place, and cannot decide whether the potential contribution of this mechanism constitutes a major or a trivial aspect of the intraocular fluid transport.

It is not easy to find an experimental approach that could be expected to allay these doubts and uncertainties. A possible road, however, becomes apparent from the following argument. The oxidative chain which we have postulated, connecting the oxidase enzymes of the epithelium to the boundary and the boundary to the dehydrogenases of the stroma, must consist of many links. If one

could identify some of these links, if one could find experimental procedures by which a given link could be removed from the system and then readministered, it might be possible to show that the set of phenomena that we have linked in theory—anomalous dye transport, redox potential of the epithelium and of the stroma, and water transport—are conjointly altered in the manner expected from the theoretical considerations outlined above.

Time does not suffice to report on this phase of our studies,[19, 21] but it may be stated in summary that adrenalin and ascorbic acid each appear to contribute a link in the intercellular redox chain. Adrenalectomized animals (protected against cortin deficiency) and animals on a vitamin-C deficient diet show marked and similar changes in the physiology of their ciliary processes. Anomalous dye transport ceases. The redox potential of the epithelium rises and that of the stroma falls, indicating a decrease in the rate of reduction in the epithelium and a decrease in the rate of oxidation in the stroma. Water transport into the eye is reduced as can be shown in experiments on the reformation of the aqueous after removal of some of the intraocular fluid. All these phenomena occur at a time when the animals show no gross signs of debility as the result of the experimental procedure, and all are back to the normal state immediately on administration of the defective substance.

The results of these experiments lend very strong support, indeed, to the interpretations we have given, and indicate that the contribution of the mechanism that we have described to the intraocular fluid transport is a very significant and not a trivial one. Moreover, the role which this interpretation assigns to ascorbic acid leads to a simple and ready explanation of the mechanism of intraocular ascorbic acid secretion.

This brings the account of our studies to a suitable resting place, but it is not to be presumed that we have reached a satisfactory and full account of the secretory mechanism.

Our knowledge of the secretory boundary is very incomplete. The apparent activation of a redox chain by adrenalin raises questions regarding the pharmacologic mechanisms of adrenergic action that are at once fascinating and difficult to approach. [23, 24, 28] No data are, as yet, available to indicate whether or not the synthesis of the ocular mucoid is linked to the secretory mechanism that we have described.

Moreover, even if we have a full knowledge of how each component of the intraocular fluid is transferred across the secretory boundary, we would still stand only on the threshold, for the secretory organ that we have so far identified can act only on the fluid and solutes in the ciliary stroma. Transfer from plasma to extravascular fluid spaces in the ciliary stroma is required in order to make fluid and solutes available to the secretory organ. Since the classical studies of Starling,[45] it has been assumed that osmotic and diffusional forces suffice to explain the transfer across the capillary wall, but the inadequacy of such assumptions is clear if we try for a moment to specify what happens to the capillary wall during inflammation, and under the operation of vasomotor and humoral controls. In respect to the ciliary body such neural and humoral vasomotor controls have, as yet, not even been explored.[20]

The findings so far present few implications with respect to the pathologic physiology or control of glaucoma. At most they raise the question as to whether more effort might not profitably be directed toward a reduction in the formation of aqueous in cases of glaucoma, in addition to the present approach which concerns largely an effort to increase the outflow of fluid from the eye.

May I add one final word. The picture that has emerged from our studies of a busy metabolic interaction at the boundary between epithelium and stroma in the ciliary body, and of the dependence of secretory activity upon this interaction was not in our minds when these studies were begun, but has forced itself upon us with increasing

emphasis as the work progressed. It may well
be that tissue boundaries in other organs are
sites of equally busy interactions. Recent
studies on the cornea in our laboratory have
shown that there exist complex metabolic ex-
changes and interactions between the epithe-
lium and the stroma in that tissue. The sug-
gestion that metabolic exchange and inter-

action between adjacent cells and tissues in
embryonic life may play a role in the process
of development and differentiation has been
tentatively advanced by some embryologists.
A dim but intriguing vista of integrative
relations at the intercellular level is thus
presented.

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ANIRIDIA WITH ECTOPIA LENTIS AND SECONDARY GLAUCOMA*

GENETIC, PATHOLOGIC, AND SURGICAL CONSIDERATIONS

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Aniridia or, more correctly, irideremia is the clinical absence of the iris. A rudimentary iris is usually present, but the short stump is concealed behind the corneoscleral junction. Because of its extraordinary propensities as a dominant characteristic, occasionally an irregular dominant, and because of its striking appearance which facilitates investigation, it has received extensive study by geneticists. Indeed, so interesting are its hereditary and pathologic aspects that these have received far more attention than have therapeutic measures for aniridic cases.

Moreover, the gene producing aniridia also effects different varieties of abnormalities, ectopia lentis, ectopia pupillae, abnormalities of the mesodermal and ectodermal defects of the iris, iridotasis and embryotoxon, and so forth. Thus any of these abnormalities, in either severe or mild degree, which follow no certain pattern of distribution would indicate the presence of the gene in the specific family being studied. Cases with ectopic lenses are sometimes children of parents with uncomplicated aniridia and vice versa. Those with coloboma of iris or hypoplasia of stroma occur in sibships affected with aniridia alone or with the graver condition. In Beattie's report, affected members only transmitted the disease and normal children invariably had normal offspring, which fulfills the conditions of an irregular Mendalian pattern. Falls has on record a series of dominant patterns and two pedigrees which display the abnormality inherited as a simple recessive disease. The latter is supported by the presence of consanguinity of the parents of the affected individual.

HISTORY

Barrata reported a case in 1818, and is credited as being the first to investigate this condition. Reports of aniridia then appeared with increasing frequency and, in 1898, Foster was able to collect 154 cases in the literature and added two cases of his own. Since then Collins, Waardenberg, Ida Mann, Gates, and many others have reported aniridia cases and have enlarged our knowledge of this subject. Relative papers by Beattie and by Pincus have been recently published. Of the many theories advanced for aniridia, the two most probable refer the primary fault to a failure in development of the retinal ectoderm or an aberrant development of the vascular mesoderm. Duke-Elder believes both are operative in different cases.

GENETICS AND MUTATION

The prevailing view on mutation as a direct cause of abnormality in man has been that it is an extremely rare phenomenon without practical significance. Mutation has long been recognized in lower forms of life, such as molds and yeast, and even in higher forms of life. Importance is attached to gametic mutation because it is transmitted through reproduction of the species from one generation to another; somatic mutation occurs in the body cells outside gametes and asserts itself only in one individual. In recent years the occurrence of mutation in man has been acknowledged and its form may be dominant or recessive, the later type representing 92 to 95 percent of all mutations.

Evolution is assumed to have a tendency

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to establish complete dominance of the normal type in relation to the pathologic type arising from mutation which lowers the viability of the individual. It is obvious that in man, the knowledge of whom is limited to relatively few generations and on whom no cross-breeding experiments may be performed, we shall never be able with certainty to demonstrate that a recessively hereditary disease has arisen from mutation. If a disease, which is known from experience to be dominantly hereditary, suddenly appears in a previously healthy family and afterward is inherited with regular dominance, it is reasonable to assume that the disease has arisen through mutation in one of the family concerned. Although the pathologic type may become extinct to clinical recognition after several generations, it meanwhile provides an interesting study.

Not uncommonly there occurs in a human pedigree a single, solitary eye abnormality which in other pedigrees shows marked evidence of heredity. Little is known about the proportion of such single-case pedigrees to those that show heredity, and figures based on published pedigrees generally will almost certainly understate the number of single-case pedigrees, which are less likely to be published than those which show hereditary. It is difficult to explain the presence of these solitary cases in a pedigree, whether retinitis pigmentosa, albinism, blue sclerotics, or aniridia. They occur probably in all hereditary eye conditions.

Are such manifestations Mendalian recessives linked to cases which existed in generations more remote than those to which our information extends, or is their presence the result of factor mutations in the chromosomes, or do they arise independently of the germ-plasm?

Furthermore, if the presence of a solitary case as previously defined is in some instances accounted for by the heredity alone, in other instances by environment alone, and in still other instances by the combined influence of both, what is the relative importance of these causes in hereditary eye affections?

The answer to these questions is of importance in any estimation of the inheritability of an eye affection, and it must influence opinion regarding whether any of the progeny are likely to be affected or not. Also, it may materially alter our conception of the proportion of single-case pedigrees to those showing inheritance.

The disease of aniridia is generally inherited from affected members of a family in a proportion of approximately 50 percent. In this study, 3 in the first generation were affected, and 6 in the second generation, amounting to a little less than 50 percent of the first member known (fig. 1). Being a dominant characteristic the trait becomes apparent as a heterozygote. There are no cases reported of two heterozygotes for the condition marrying each other and it is therefore impossible to say what appearance a homozygote for the condition would present. It is possible that lethal genes would accompany the homozygote condition. Infertility does not seem to accompany aniridia; in fact, the pedigrees reported are relatively prolific.

It can be assumed that in some ancestor the condition arose as a gene-mutation, and thereafter, as in other alterations of the germ plasm, the defect was transmitted in accordance with Mendalian principles. Nothing is known of the cause of gene mutations in human beings or indeed of mammals generally, but in the insect world the normal production of mutations can be multiplied by means of thermal or X-ray stimulation of the germ plasm. Stevenson and others have reported cases of aniridia without known affected ancestry, and in such cases it would seem that a new mutation must be postulated.

In recent years an attempt has been made to assess the mutation rate of various human abnormal conditions. J. B. S. Haldane began this work with the calculation of a mutation rate for hemophilia. Mollenbach has esti-
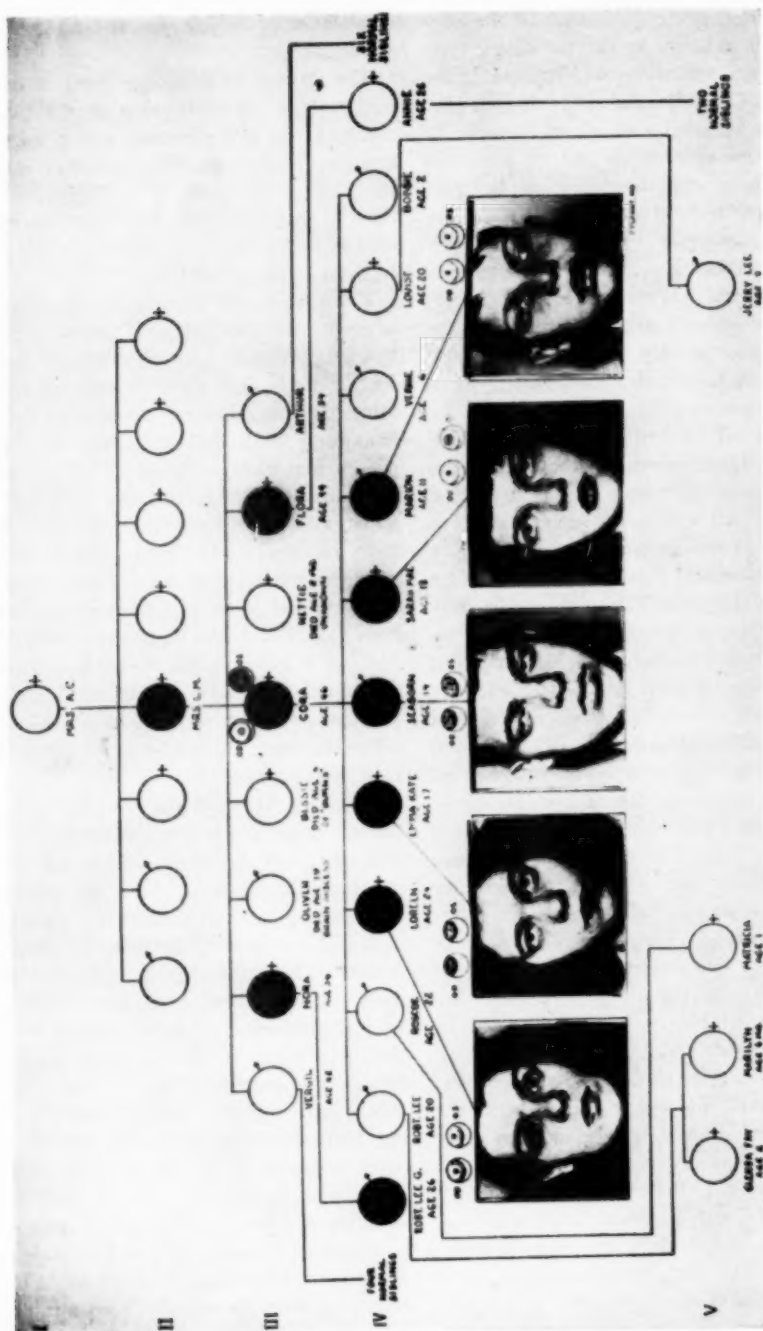
Fig. 1 (Callahan). Pedigree of aniridia family. Note that Generations III and IV are not arranged chronologically, but are altered to save space. However, proper ages are given.

mated the mutation rate for aniridia, on the basis of his findings in Copenhagen, to be between 1:50,000 and 1:100,000. Falls believes this estimate to be satisfactory.

CLINICAL APPEARANCE

Since no iris is visible, the "pupil" is as large as the cornea. Photophobia is present and poor vision is usually but not always the rule. In the absence of other abnormalities the frequent occurrence of low visual acuity may be accounted for by the fact that clinical and pathologic examinations have shown that sometimes the fovea is absent. Alger proposed the theory that in cases in which the macula is anatomically present, since refraction of light both outside and inside the equator of the lens without the iris diaphragm causes poor images, this lack of precision may deprive the macula of effective stimulation in the early months of life when normal development takes place.

Additional ocular anomalies are common, and these cases have cloudy corneas and ectopic lenses, which are cataractous. All eyes have or have had secondary glaucoma which has continued for years, increasing the size of the eye, and decreasing the vision.

PATHOLOGY

The first pathologic report of an aniridic eye was that of Pagenstecher who showed that at least a rudimentary iris was nearly always present. Treacher Collins reported his findings on three aniridic eyes. Two of these were removed from individuals with double aniridia, in each of whom a corneal ulcer perforated in one eye, and the development of subsequent secondary glaucoma necessitated removal of the eye. In the first of these the ciliary body ended anteriorly in a rounded, slightly projecting nodule which, although not sufficiently large to be seen through the cornea, was present, and was pushed forward in contact with the posterior surface of the cornea and was blocking the filtration angle. In the second the iris was represented solely by a small

rounded projection on the anterior surface of the ciliary body. The filtration angle of the cornea was blocked by the intimate adhesion of this projection.

The third case was of traumatic aniridia followed by secondary glaucoma and the eye was removed 12 years after the accident. The eye had remained blind since the accident and during the last 3 years had gradually increased in size, and was staphylomatous. The anterior part of the cornea showed some round-cell infiltration and new vessels between its layers. Besides other findings it was observed that the iris had been torn away at its extreme root. The ciliary body was very atrophic and the most anterior of the anterior processes of the ciliary body was intimately adherent to the posterior surface of the cornea at its periphery in the region of the ligamentum pectinatum.

Lembeck reported a case in which the rudimentary iris was enclosed between two lamellae of Descemet's membrane and had formed an abnormal union with the cornea and sclera. One of the lamellae of Descemet's membrane passed beneath the iris to which it had grown fast and was lost in the ligamentum pectinatum, while the other passed down over the posterior surface to cover the imperfectly developed ciliary bodies. The uveal part of the iris lay stretched out on the cornea to a greater distance than the retinal part in which one could easily recognize two layers.

We were fortunate in persuading the eldest affected child to permit us to remove her blind eye for examination and Dr. T. E. Sanders has kindly furnished us with the pathologic study.

A rudimentary iris is present (fig. 2) which varies slightly in size but is about 1 mm. in length. Here the iris is inserting into the face of the ciliary body, but in most of the sections the iris is in contact with the posterior surface of the cornea, forming a dense peripheral anterior synechia.

Except for this small rounded tip, the
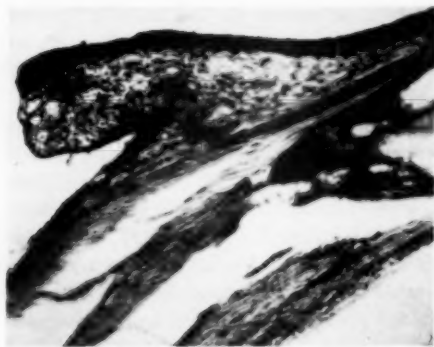
Fig. 2 (Callahan). A rudimentary iris is present, which varies slightly in size but is about 1 mm. in length. Here the iris is inserting into the face of the ciliary body, but in most of the sections the iris is in contact with the posterior surface of the cornea, forming a dense peripheral anterior synechia. Except for this small rounded tip, the iris stroma is so atrophic that it can hardly be recognized. The area of stroma not in contact with the endothelium is extremely fibrotic and there is no evidence of differentiated muscle groups although muscle fibers are present. Both the greater and lesser circular anastomoses of the anterior ciliary vessels are present.

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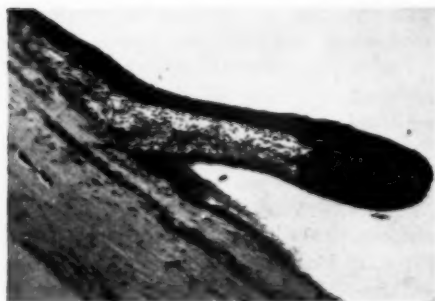
Fig. 3 (Callahan). Another section of the iris root. There is no evidence of the canal of Schlemm or spaces of Fontana. It is impossible to determine the condition of the filtration angle structures because this area is almost completely atrophic.

and lesser circular anastomoses of the anterior ciliary vessels are present.

On the opposite side of the same section, the iris root looks somewhat different (fig. 3). There is no evidence of the canal of Schlemm or spaces of Fontana. It is impossible to determine the condition of the filtration angle structures because this area is almost completely atrophic.

A section taken longitudinally through the optic nerve (fig. 4) shows the deep cupping resulting from increased ocular pressure and nerve fiber atrophy. A transverse section through the optic nerve well back from the globe (fig. 5) shows complete atrophy of nerve fibers with columnar
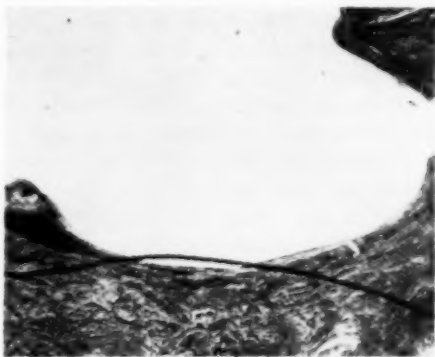
Fig. 4 (Callahan). Section taken longitudinally through the optic nerve showing the deep cupping resulting from increased ocular pressure and nerve-fiber atrophy.

replacement gliosis. There is moderate passive congestion of all vessels present. The sheath of pia-arachnoid surrounding the central vessels is well outlined and one corpus amylaceum is present.

Dr. Sanders has allowed us to include in this report a pathologic specimen of an aniridia from his collection (WU-2928). This is a case of true aniridia (fig. 6). There is complete absence of the iris. The ciliary body is atrophic but the longitudinal fibers of the muscle may be seen. The secretory epithelium is present but the cells are flatter than

Fig. 5 (Callahan). Transverse section through the optic nerve well back from the globe showing complete atrophy of nerve fibers with columnar replacement gliosis. There is moderate passive congestion of all vessels present. The sheath of pia-arachnoid surrounding the central vessels is well outlined and one corpus amylaceum is present.
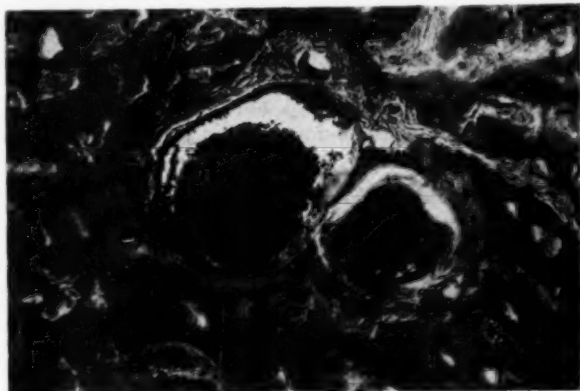
are usually seen. The canal of Schlemm is well outlined and contains a few red blood cells. The ciliary body attaches to the scleral spur in a normal fashion. On the other side of the eye, the cuboidal secretory cells show more activity (fig. 7). The ciliary processes are normal in outline. The scleral spur is not readily identified nor are the structures at the iris angle normal.

PHYSIOLOGY

Why the presence of an ectopic lens greatly increases the tendency to glaucoma is not certain. In congenital ectopia lentis without aniridia the incidence of glaucoma is low. It seems to us that in aniridia with ectopia lentis the condition is more severe, and the adhesion of the rudimentary iris to

Fig. 6 (Callahan). (Case WU-2928). True aniridia, complete absence of the iris. The ciliary body is atrophic but the longitudinal fibers of the muscle may be seen. The secretory epithelium is present but the cells are flatter than are usually seen. The canal of Schlemm is well outlined and contains a few red blood cells. The ciliary body attaches to the scleral spur in a normal fashion.

Fig. 7 (Callahan). (Case WU-2928) (Second section). The ciliary processes are normal in outline. The cuboidal secretory cells show more activity than in Figure 6. The scleral spur is not readily identified nor are the structures present at the iris angle normal. This figure contrasted with Figure 6 shows how variable the ocular structures are in this case.
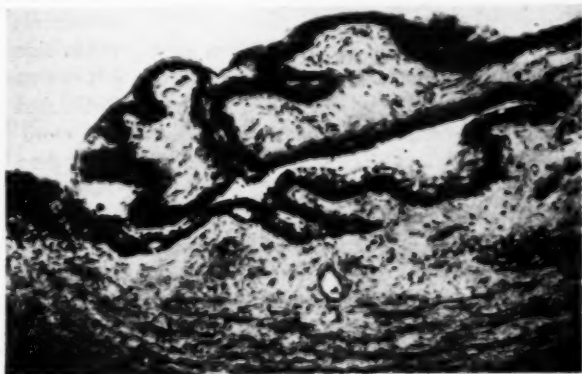
the cornea may be more complete in such cases. In our series, glaucoma has occurred in cases without ruptured zonules similarly to those cases with ruptured zonules. The lens may be responsible for exerting pressure against the ciliary processes and rudimentary iris in some cases. In the one case in which the lens was removed, most of the lens material was extruded upon completion of the limbal section. A severe postoperative reaction with ocular hypertension developed and required several paracenteses. The remainder of the lens absorbed, but the inflammatory reaction continued for three months.

The iris normally has some function in the interchange of fluids in the eye, and its absence may have a deleterious effect. The ciliary processes are atrophic and it is probable that less aqueous than normal is formed. If so, perhaps aniridic eyes have a metabolic rate lower than normal. Observations on the appearance of fluorescein in the aqueous after its intravenous injection were inconclusive. In one instance it appeared one minute after intravenous injection, but in another it did not become apparent even after observation for a period of one hour and a half. Possibly the absence of the constant contraction and dilatation of the iris may remove a normal stimulus and be responsible for a more sluggish circulation of the aqueous.

CASE REPORTS

A mother and 5 of her 10 children have double aniridia, hazy corneas, and cataractous lenses. All of the affected 5 children have ectopic lenses and glaucoma, 3 have external strabismus of about 45°, and 4 of the 5 have nystagmus. The defect has occurred without regard to sex or chronology.

There are other affected sibships living, which are being verified. The genealogy of the family is shown in Figure 1. The ectopic lenses follow an interesting pattern of position; all of them are partly cataractous, some advanced. The gene producing aniridia has

been fairly constant in that all forms have been about the same, and no mild forms, such as coloboma of the iris, have been observed.

The optic nerve and gross fundus details can be seen in several eyes with external illumination, because only aqueous and vitreous intervene between the cornea and the retina. All corneas have generalized opacities with haze, and this has prevented successful gonioscopic examination.

Photophobia has not been a problem in this study for, although the children replied to questioning that they were sensitive to light, they have preferred not to wear shaded lenses which were repeatedly supplied. Tattooing of the cornea has been reported but in our cases the glaucoma and the haziness of the corneas prevented such considerations. The nystagmus ruled out the use of contact lenses with painted irides.

Prior to our first observation of the family in June, 1946, no ocular surgery had been performed. In all eyes, the operative site was recorded in detail to prevent a secondary or a tertiary operation from occurring at the site of the primary operation.

All eyes have shown a complete lack of response to pilocarpine, eserine, and similar drugs. The clinical examination and course of each individual are presented in the following case reports.

Case 1. Cora, the mother, aged 48 years, has vision of: R.E., 20/200; L.E., hand movements at 3 feet. She has had poor vision since birth. Seventeen years ago, the left eye was struck by a stick, which further diminished vision, and it has deteriorated still more in last two years. Both corneas show deep vascularization at the periphery. The right lens has a posterior cortical cataract; the left, a mature cataract. The zonular system cannot be seen in either eye. Nystagmus is present. The tension is: R.E., 30 mm. Hg; L.E., 22 mm. Hg. This patient has been unwilling to undergo surgery.

Case 2. Loreen, aged 24 years, has vision of: R.E., 9/200; L.E., blind. Poor vision

has been present since birth; the left eye has been blind for several years. There was no injury of either eye. The right cornea shows diffuse opacities more numerous at the epithelium, with central superficial bullous keratitis. The lens shows an anterior and posterior cortical cataract, with more opacities in the axial region. The zonular system is intact inferiorly. The periphery of the fundus, as seen through the aphakic area,

tension, and the patient consented to the enucleation to provide material for microscopic study.

Case 3. Emma Kate, aged 17 years, has vision of: O.U., 10/200. She has had poor vision since birth, but it has diminished in the past few years. The patient's coöperation has been difficult to maintain, and she would not attend the clinic even for observation in 1947. Both corneas show generalized
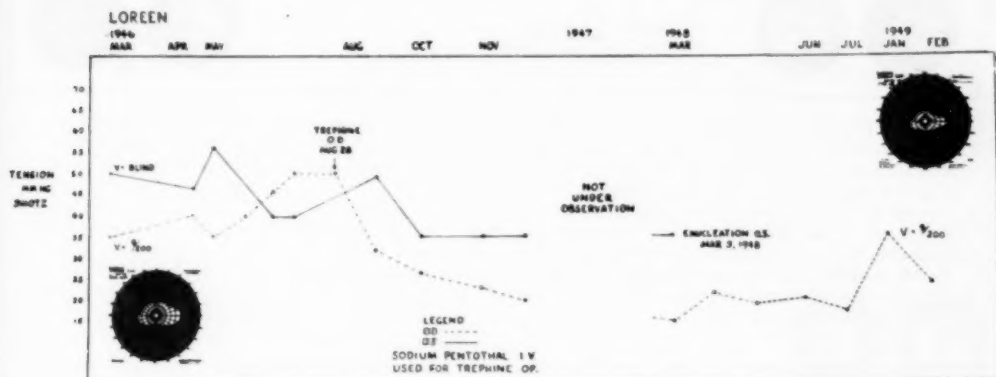
Fig. 8 (Callahan). Clinical course of Loreen. The tension became lower after trephination of the right eye in August, 1946. In late 1948 it increased, and the reduction in January, 1949, may or may not be due to the intravenous administration of sodium pentothal anesthesia for 20 minutes, no surgery being performed. The visual acuity has not decreased, but the visual field has contracted moderately. She consented to removal of the left eye to provide material for pathologic study.

seems normal. The corneal opacities obscure details. The left eye exhibits the same findings and, in addition, the optic nerve shows advanced atrophy with deep cupping.

Clinical course(fig. 8). A trephination was performed on the right eye in August, 1946, and this has been followed by a satisfactory lowering of tension. In late 1948 the tension increased, the stimulus being unknown. The reduction in January, 1949, may or may not be due to the administration of sodium pentothal anesthesia intravenously for 20 minutes, no surgery being performed. During the course of observation, the visual acuity has remained 9/200, and the visual field has contracted slightly. The left eye was not painful despite the greatly elevated

opacities. The lenses are ectopic, and in each eye the lower margin of the lens extends from about the 9-o'clock position on the limbal margin to about the 1-o'clock position. Generalized capsular opacities occur in both lenses. The fundi, observed through the aphakic area, appear normal.

Clinical course (fig. 9). Following a trephination of each eye and a cyclodiathermy of the left eye during mid-1946, the tension became elevated toward the end of the year, and probably remained so during 1947. In March, 1948, a cyclodialysis was performed on the right eye, but it was not successful in lowering the tension. Several paracenteses were done, and in April, 1948, the cataract was removed through an ab externo incision.
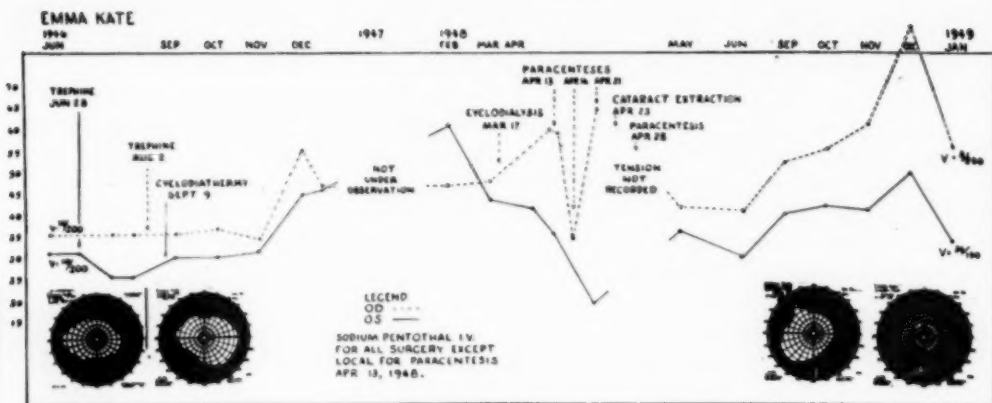
Fig. 9 (Callahan). Clinical course of Emma Kate. Following a trephination of each eye and a cyclo-diathermy of the left eye in mid-1946, the tension increased and probably remained so throughout 1947. A cyclodialysis of the right eye in March, 1948, increased the tension in the right eye and at the same time the tension in the left eye decreased. In April, 1948, the cataract of the right eye was removed through an ab externo incision, and about two thirds of the lens material was immediately extruded. Prolonged ocular reaction followed for several months. The tension has remained abnormally elevated since the operation, and has fluctuated widely without apparent cause. The vision has decreased from 10/200 to 2/200 and no lens correction improves the acuity. In the left eye the tension has varied con-siderably and has remained elevated despite two surgical procedures. It has retained acuity of 10/200 and about the same visual field.

About two thirds of the lens was immedi-ately extruded. No vitreous was lost, and irrigation of the retained lens material was then considered unwise. The remainder of the cortical material slowly absorbed, an aqueous flare remaining for 6 weeks after surgery. The ocular reaction continued for 3 months. The tension has fluctuated widely, the cause being unknown. The acuity has decreased from 10/200 to 2/200. The tension
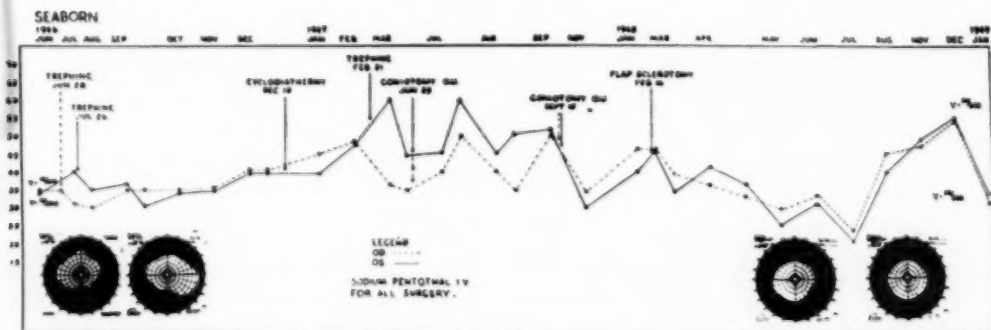
Fig. 10 (Callahan). Clinical course of Seaborn. The inadequacy of all glaucoma surgical procedures is apparent. In this case, also, a rise in tension followed the cyclodiathermy. The flap sclerotomy of the left eye in February, 1948, has been followed by a gradual lowering of tension and, as is true in many instances in this series, surgery of one eye has been followed by lowering of tension of both eyes. The cause of the elevation of tension in late 1948 is unknown, and the reduction may or may not be due to the intravenous administration of sodium pentothal for 20 minutes, no surgery being performed. The visual acuity has remained about the same, and the visual fields have contracted slightly.

in the left eye has varied considerably, and has remained elevated despite two surgical procedures. The eye has retained an acuity of 10/200 and about the same visual field area.

Case 4. Seaborn, aged 14 years, has vision of: O.U., 10/200. Poor vision has been present since birth, and he has complained some of photophobia and painful eyes. Both corneas show generalized opacities, involving all layers. The lenses are ectopic and, in each eye, the zonular system is ruptured

the elevation in late 1948 is unknown, and the reduction may or may not be due to the intravenous administration of sodium pentothal for 20 minutes, no surgery being performed. The visual acuity has remained about the same, and the visual fields have contracted slightly.

Case 5. Sara Mae, aged 13 years, has vision of: O.U., 10/200. Although she has had poor vision since birth, she has noticed no recent diminution of vision. Mild photo-
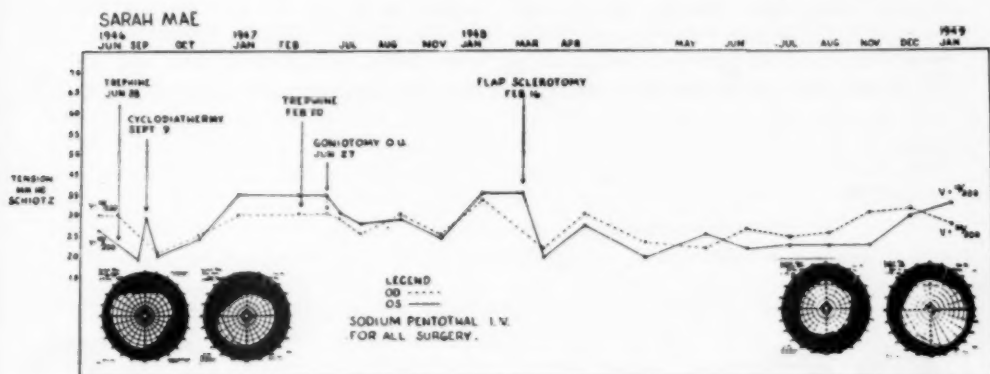
Fig. 11 (Callahan). Clinical course of Sara Mae. The trephinations and cyclodiathermy in late 1946 and early 1947 did not control the tension. Goniotomies in June, 1947, also failed to control the tension. A flap sclerotomy of the left eye in February, 1948, has been followed by a fairly satisfactory tension level. The vision has remained about the same and the fields have not diminished.

from about the 8-o'clock position on the limbal margin to the 4-o'clock position. Vitreous seemed to be almost in contact with the posterior surface of the cornea. The details of the fundi which could be seen were apparently normal, but no foveal reflex could be observed. Nystagmus is present.

Clinical course (fig. 10). The general inadequacy of all surgical measures is apparent, and in this, as in the preceding case, a rise in tension followed the cyclodiathermy. The flap sclerotomy of the left eye done in February, 1948, has been followed by a gradual lowering of tension. In this graph may be noted the general tendency of both eyes to follow the same curve, even though only one eye is operated upon. The cause of

phobia and lacrimation are present. Both corneas show relatively infrequent corneal opacities, generalized in distribution. The lenses are ectopic, the lower edge of the equator showing opposite the limbus from about the 9-o'clock to the 3-o'clock positions in the right eye, and from the 9-o'clock to the 1-o'clock positions in the left eye. Lens opacities are moderately advanced in the right eye, and more marked in the left; they are located chiefly in and near the posterior capsule. Vitreous does not present toward the cornea, perhaps because the zonular system is intact in both eyes. At the lower portion of each optic nervehead there is an inferior crescent. Nystagmus is present. There is external strabismus of 45°,

with tendency to fix with the right eye.

Clinical course (fig. 11). The trephinations and cyclodiathermy in late 1946 and early 1947 did not control the tension. Goniotomies were performed in mid-1948, but were not successful in controlling the tension. Because of the corneal haziness, it is difficult to see the rudimentary iris and to locate the chamber angle. A more basic reason for the failure of all goniotomies may be that at the age these children have reached, in all probability the constantly increased intraocular tension has caused

position. Vitreous seems to be almost in contact with the posterior surface of the cornea. The fundal details appeared normal, but the foveal reflex could not be seen. Nystagmus is present. There is alternating external strabismus of 45°.

Clinical course (fig. 12). In the youngest affected child the tension has followed a fairly satisfactory course, and only three surgical procedures have been performed. The visual acuity has decreased slightly, and the visual fields have remained approximately the same.
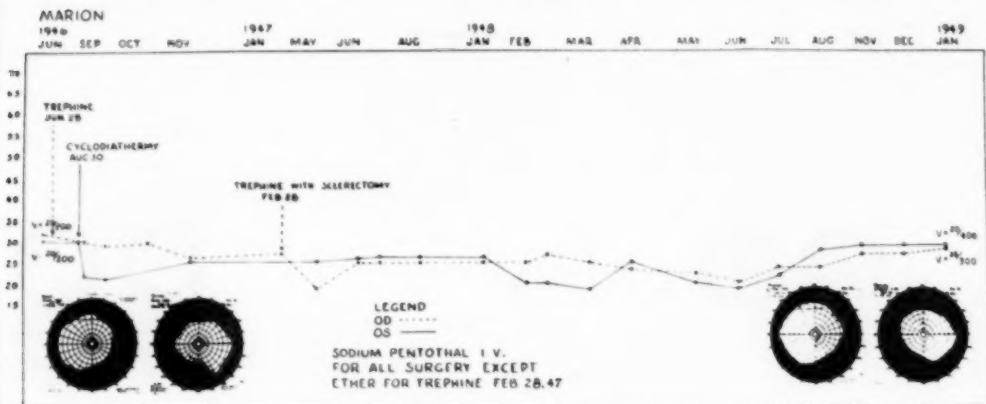
Fig. 12 (Callahan). Clinical course of Marion. In the youngest child, the tension has remained lower and more constant. Three surgical procedures were performed. The visual acuity has decreased slightly and the visual fields have remained approximately the same.

obliteration of any semblance of Schlemm's canal that may have been present. A flap sclerotomy on the left eye in February, 1948, has been followed by a fairly satisfactory tension level. The vision has remained about the same, and the visual fields have not diminished.

Case 6. Marion, aged 11 years, has vision of: O.U., 20/300. He has had poor vision since birth, but has noticed no diminution. Both corneas show generalized opacities, involving all layers. The lenses are ectopic, and in each eye the zonular system is ruptured from about the 7-o'clock position on the limbal margin to about the 5-o'clock

DISCUSSION

Most of this family attend the State Blind School and it is planned to follow all individuals for a decade. Another report is planned after several years, and at that time it is likely that there will be more members of the family. Some of these may be affected.

The disordered physiology of the formation of aqueous and its elimination is not at all clear. In the eye subjected to pathologic examination, the canal of Schlemm and the spaces of Fontana are entirely absent. In the other eyes it can be reasonably

assumed that the rudimentary iris is adherent to the cornea, obstructing the angle. In both pathologic specimens, the ciliary processes are atrophic, and it would seem likely that aqueous is formed slowly, thereby conducting the metabolism of the eye at a lower rate than normal. Meller and others have proposed the theory that much of the absorption of the aqueous is performed by the crypts of the iris, and the lack of this absorptive surface may be another factor in the production of glaucoma.

Few surgical experiences in controlling the glaucoma in aphakia have been reported, but a few investigators have noted their results in operating upon cataractous ectopic lenses in aphakia. Treacher Collins removed such a lens, and the patient regained 20/100 acuity with a plus-16 lens. Discissions have been performed in young children, and Beattie suggested an intracapsular extraction to avoid the lens protein reaction. This was our plan in the one cataract extraction performed, but upon completion of the ab externo incision over the ectopic lens, the lens material was immediately extruded, and, to avoid vitreous loss, the McLean sutures were pulled taut and tied. This is the only eye in which considerable vision has been lost.

Few conclusions can be made after following these cases for two and a half years, but a few observations are advanced.

1. The general inadequacy of the various types of glaucoma surgery is apparent. Cyclodiathermy is particularly contraindicated, since in three instances the tension increased and in one it did not change. Goniotomies are also contraindicated, probably because the canal of Schlemm, if present at birth, has become obliterated by the long-continued increased pressure.

2. The similarity of tension curves of both eyes in the same patient, regardless of which eye is operated upon, is noteworthy. They show that in several instances in which the tension became elevated, the unoperated eye has a similar or even greater lowering than the operated eye. This raised the question that perhaps factors other than surgery might be responsible. It might be the factor of relaxation provided by the general anesthetic, or the action of the sodium pentothal on the ciliary body. Several times on three of the patients, sodium pentothal has been administered intravenously for 20 minutes, no surgery being performed. The results are inconclusive, because the pressure dropped in some instances immediately and later in others. However, a general trend downward over the course of a month occurred in all three cases. Our present plan for the future management of these cases is to give sodium pentothal intravenously for 20 minutes, and not to operate.

3. These eyes seem to withstand the elevated pressure better than glaucomatous eyes usually do, as shown by the relatively small loss of visual fields despite the greatly increased intraocular pressure.

Medical College of Alabama (5).

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DISCUSSION

DR. DAVID G. COGAN (Boston, Massachusetts): To start the discussion, I would like to ask Dr. Callahan if he has any suggestions as to why glaucoma should develop late in these cases of aniridia, when presumably it is based on a congenital defect? Is there any evidence in the specimen of a progressive lesion which has occurred postnatally?

DR. K. W. ASCHER (Cincinnati, Ohio): I wonder whether aqueous veins were found in the eyes of the members of this interesting family? In eyes like these, observation of the aqueous veins and of the aqueous-humor elimination might yield interesting results.

A second question: on eyes with a desperate prognosis like this, could one try one of the toxic depressants of intraocular pressure, erythrophleine or nervocidine? Besides an inflammatory reaction, they produce corneal anesthesia and a long-lasting hypotony. In eyes responding to miotics, I would not use these drugs but in eyes which are doomed to become blind, it might be justified to use one of these powerful drugs.

DR. CONRAD BERENS (New York City):

I should like to ask Dr. Callahan if he has had any great difficulty with bullous keratitis in these cases?

I have had two patients on whom I have tried to perform superficial keratectomy. In both cases, I have had great vascular reactions and I have had no success in maintaining transparency of the cornea. One case is under observation now and I would appreciate help.

DR. CALLAHAN (closing): It seems likely that glaucoma is present at birth or develops soon afterward, and the condition gradually becomes more severe. There is no evidence in the specimen of a progressive lesion except that continued tension has thinned out all layers and obliterated Schlemm's canal. So severe is the corneal haze that aqueous veins, if present, were not visible. The chamber angle could not be seen with the gonioscope. The suggestion for the use of a toxic depressant of intraocular pressure is appreciated, and will be used with the indications as suggested by Dr. Ascher.

Bullous keratitis has not been present in our cases of aniridia.

A GENE PRODUCING VARIOUS DEFECTS OF THE ANTERIOR SEGMENT OF THE EYE*

With a pedigree of a family

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Ann Arbor, Michigan

Genes producing developmental anomalies are well known for their diversified effects upon different individuals within a family. This appears to be particularly true of those genes causing structural defects in the anterior segment of the eyes.[1-8] Seldom, however, does one see such a wide variety of pathologic changes as was demonstrated by the single family reported herein. In this kindred, the inheritance is due to a single dominant gene which has resulted in varying combinations of the following abnormalities: congenital corneal opacity, embryotoxon, corectopia, pseudopolycoria, slit-pupil, iridotasis, dyscoria, ectopia pupillae, ectopia lentis, anterior polar cataract, and hydrophthalmos. An increased intraocular pressure was observed in the majority of the affected individuals, and, in cases where gonioscopy was performed, abnormal tissue (? mesodermal) was found to occupy the anterior-chamber angle. There is, in addition, some evidence that the gene also may produce a defect in the hearing sense.

Method of study

The investigation of this family was initiated by the appearance at the University of Michigan ophthalmological clinic of a brother (G-5) and sister (G-9) on November 27, 1940. Both of these patients had previously visited the clinic on separate occasions and a careful review of their histories indicated the presence of similar ocular pathologic changes in their antecedents and collateral relatives. Subsequently a careful pedigree was obtained from A-2.

With the pedigree serving as a work sheet all living members were examined with the exception of A-4 who refused examination. The greater number of the examinations had to be carried out in the homes of the patients under rather difficult conditions. Many medical prejudices as well as general apathy had to be overcome before even an interview could be obtained in certain branches of the family.

The examinations performed consisted of a complete ocular examination and a series of genetic test factors. The latter included serologic tests of blood and saliva, determination of the taste reaction to phenyl-thio-carbamide, tests of color vision and ocular dominance. The blood samples were tested with respect to the blood groups O, A, A_1, A_2, and B, and the M and N types. The "secretor factor" was determined on the saliva by means of human A and B serum and anti-O ox serum. Data on these known hereditary characters are of interest primarily in regard to their genetic linkage. No evidence of linkage between these test factors and the gene studied in this family was uncovered.

Pedigree

This pedigree chart (fig. 1) follows that of conventional diagrams by arranging the children of a single union horizontally and

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● ANTERIOR SEGMENT OCULAR
   DEVELOPMENTAL ANOMALIES
◐ REPORTED AFFECTED
◙ EXAMINED NORMAL
◎ REPORTED NORMAL
○ NO INFORMATION
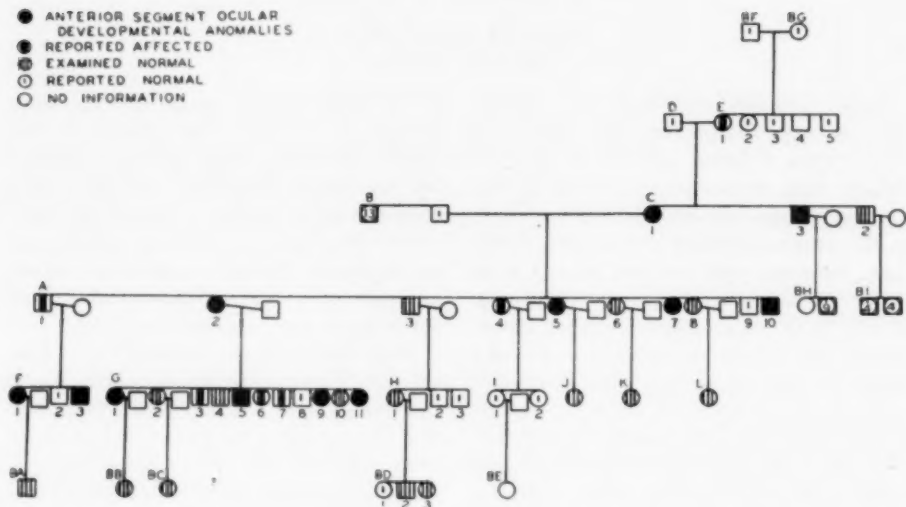
Fig. 1 (Falls). Pedigree chart showing occurrence of ocular defects in four generations of a family.

ANTERIOR SEGMENT DEVELOPMENTAL ANOMALIES
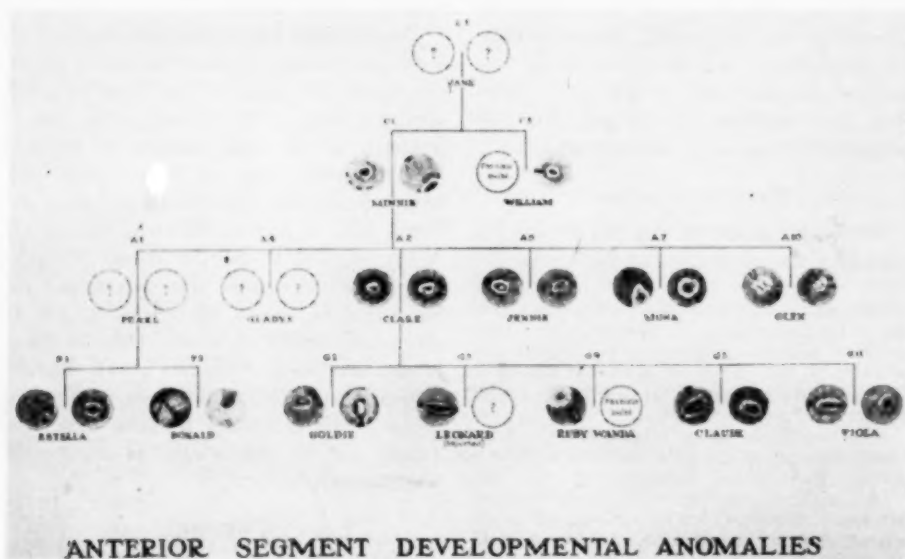
Fig. 2 (Falls). Chart showing pathologic changes in various members of the family.

in order of their birth. Information is available concerning four affected generations, the first being known only through historical evidence provided by the living descendants. Genealogic evidence concerning the spouses was only incompletely obtained and it is therefore not definitely known if the respective unions are free from consanguinity. At least it was denied in most instances.

The ocular anomalies in this family are transmitted in a characteristic dominant Mendelian pattern. A dominant gene will be transmitted by an affected parent to an anticipated 50 percent of his or her offspring. It is also to be expected, in turn, that an affected person will have one affected parent. The normal siblings of involved individuals, as well as normal offspring of the latter, will have children normal in respect to the trait in question. This pedigree indicates that the gene being studied in this family fulfills all of the specified prerequisites of a dominant inheritance pattern.

PATHOLOGIC CHANGES

E-1

Family reports, substantiated by a very incomplete hospital record, indicate that this woman was very probably affected and that she was responsible for the transmission of the defect to all cases subsequently described. She was reported to have had large eyes which "bulged out" like those of her daughter, C-1, and the corneas were said to be "milky-white" in color.

Vision had always been poor and for many years the patient experienced severe ocular and head pains associated with blurred and distorted vision. She was finally forced to consult an ophthalmologist. Dr. Walter Parker initiated surgery in both eyes for relief of her glaucoma, a diagnosis of "buphthalmos" having been made. Total blindness ensued several years before her death at the age of 74 years. She also suffered in later years with a rather marked loss of hearing. The patient was described as short and stocky, of dark complexion and with "dark chocolate brown" iris color.

C-1

This obese, 70-year-old woman insisted that she had had no difficulty with her eyes until she was nearly 14 years of age. Short periodic attacks of blurred vision were then experienced in combination with rather severe frontal head pains. Many pairs of glasses were worn but failed to relieve

her symptoms or materially improve her visual acuity. All useful vision had been lost 20 years prior to our examination. The woman was short in stature and rather darkly pigmented. No signs of von Recklinghausen's disease could be observed. Her blood pressure was 165/85 mm. Hg. The patient was hard of hearing, otosclerosis having been previously diagnosed and a hearing aid prescribed by a local otologist.

Ocular findings. The vision was nil in both eyes, and there was marked divergence of the visual axes. Ocular movements could not be obtained due to loss of fixation. The corneal diameter in the right eye was 13.5 mm. horizontally and 13.0 mm. vertically; and in the left eye, 13.0 mm. horizontally and 12.5 mm. vertically. A rather pronounced scleral over-riding was evident in both eyes.

The corneal surfaces presented an opalescent color in which was interspersed small dark-gray, calciumlike deposits, the latter being more conspicuous in the palpebral fissure area. The entire anterior segment was grossly enlarged in both eyes. The sclera anterior to the equator was so thin as to have a distinct bluish cast. The exophthalmometer reading (Hertel) was 18.5 mm., O.D., and 22 mm., O.S.

Right eye. Transillumination revealed an irregular but nearly centrally placed pupil, with marked prominence of the sphincter. The iris stroma was extremely atrophic. Inferiorly and temporally the iris seemed adhered to the corneal surface despite the presence of an abnormally deep anterior chamber. The lens appeared cataractous. The tonometer tension was 36 mm. Hg (new Schiøtz).

Left eye. Visualization of the inferior portion of the anterior chamber was possible through the macular and nebulous scarring of the cornea. The anterior chamber was deep and large. A portion of the sphincter could be seen at the 5-o'clock position, at which point it seemed adhered to the cornea and angle. An iris dehiscence or small iridotasis was observed near the periphery at the 11-o'clock position. The iris stroma was attenuated and nearly absent except for the pigment layer. The tonometer tension was 36 mm. Hg (new Schiøtz).

C-3

This dark-complexioned, well-developed, 72-year-old woodsman was examined in his bed to which he had been recently confined by a heart attack. The patient stated that his right eye had been injured in a logging accident at the age of 18 years and that vision in this eye failed completely within one month. During the last five years there had also been a gradual loss of vision in the left eye, and the patient recalled occasional colored halos and blurred vision associated with mild ocular discomfort. The blood pressure was 155/85. mm. Hg.

Right eye. The corneal horizontal diameter was 7.5 mm. The entire cornea was leukomatous and vascularized, and its surface was flattened. The entire eye was small and the globe was cuboidal

in outline. The tonometer tension was 8 mm. Hg (new Schiøtz).

Left eye. The uncorrected visual acuity was 6/12—2. The corneal diameter was 12.5 mm. horizontally and 12.0 mm. vertically. The corneal stroma was clear except for nearly complete arcus senilis, and the anterior chamber was of normal depth. The iris color was hazel; the stroma was moderately well developed but presented a certain degree of atrophy which permitted visualization of the pigment layer. The lesser arterial circle of the iris was incomplete, but the iris sphincter was abnormally well seen through the attenuated stroma. The pupil was oval and irregular. Pupillary reflexes were prompt. The lens was clear except for cuneiform opacities at the inferior nasal periphery. A few strandlike vitreous opacities were present.

The optic nervehead was pale and moderately cupped with a fair preservation of the nasal tissue. The retinal vessels were arteriosclerotic. The macular area and retinal periphery were normal except for prominence of the choroidal vasculature and choroidal verrucae. No unusual degree of choroidal arteriosclerosis was noted. The tonometer tension was 32 mm. Hg (new Schiøtz). The confrontation field suggested a moderate concentric peripheral contraction.

A-1

This man died as a result of a cerebrovascular accident several years before the initiation of this investigation. Bilateral iridectomy had been performed by a Chicago physician in 1923, but no records are available, except that a diagnosis of glaucoma had been made. This man's eyes were described as very large, with prominent opalescent corneas and chocolate-brown irides, and the pupils were eccentrically placed. Severe ocular pain had been experienced most of this man's life, and this was not relieved by surgery. No nystagmus was known to have been present. His visual acuity was very poor both before and after the operation. Auditory acuity was "good."

A-2

This 51-year-old woman had been gradually losing her visual acuity for several years, but seemed strangely euphoric about it. Only mild remorse was expressed over the fact that so many of her children were blind or nearly so. This woman was well developed, slightly obese, and not as darkly complexioned as her other affected brothers and sisters. She reported that she had rarely encountered any ocular discomfort but had noted some blurring of vision of her right eye.

Ocular findings. The uncorrected visual acuity was: R.E., 6/15—1; L.E., 6/30; with correction, it was: R.E., 6/9—2; L.E., 6/15—2. The eyes were straight in the primary position, with marked lateral deviation under cover. The extraocular movements were normal except for a marked overaction of the right inferior oblique muscle when looking up and to the left. The pupillary reflexes

were prompt and equal bilaterally.

The glasses worn were: +1.0D. sph. ⊃ +0.37D. cyl. ax. 65° = +2.25; +0.75D. sph. ⊃ +0.25D. cyl. ax. 180° = +2.25.

Right eye. The corneal horizontal diameter was 12.5 mm. The corneal stroma was clear and the anterior chamber was of normal depth. The pupil was irregular and oval horizontally. The anterior iris leaf was very scant and atrophic. There was no lesser arterial circle or collarette. Thin scattered radial gray strands ran from the iris base directly to the pupillary border. The pupillary sphincter was easily seen and existed as a broad band superimposed on a background of light chocolate brown. The latter was easily visualized through the nebulous or absent stroma.

Extensive anterior peripheral synechias were grossly noted between the 7- and 10-o'clock positions. The lens and central media were clear. The disc was oval horizontally, very pale in color, and showed deep glaucomatous cupping. The retinal vasculature showed signs of arteriosclerosis. The macular area, retinal periphery, and choroid were devoid of pathologic conditions. The tonometer tension was 30 mm. Hg (new Schiøtz). The confrontation visual field presented superior and nasal contracture. The exophthalmometer reading was 16 mm. (Hertel).

Left eye. The corneal horizontal diameter was slightly over 12 mm. The corneal stroma was clear, except for a gray linear deposit on the peripheral endothelial surface extending from the 2- to 4-o'clock positions. The anterior surface of the iris was adhered to this embryotoxon. The anterior chamber seemed large and deep. The pupil was triangular in outline, with the base directed temporally. The sphincter followed the outlines of the pupil and was quite broad. The anterior iris stroma was attenuated and lacking in many areas.

The pigmented iris surface was easily visualized and appeared atrophic and moth-eaten to trans-illumination. The fundus was similar to that of the right eye, except that the glaucomatous atrophy of the nervehead was less advanced. The tonometer tension was 20 mm. Hg (new Schiøtz). The confrontation field was normal. The exophthalmometer reading was 16 mm.

A-4

This short, stocky, 42-year-old woman refused examination. She considered her very poor vision to be the result of her medical contacts and was strongly prejudiced. During the course of a rather long argumentative conversation, the following observations were possible. There were at least 15 to 20 degrees of left divergent strabismus—early phthisis bulbi of the left eye.

A large cornea was present in the right eye with a corneal horizontal diameter of at least 13 mm. The cornea was partially leukomatous with band keratitis in the palpebral fissure. Pendular nystagmus of irregular amplitude was noted. The pupil was displaced superiorly and nasally and was cu-

boidal in shape. The iris sphincter was conspicuous. The iris was dark brown in color. A thin gray posterior peripheral corneal deposit extended from the 4- to 7-o'clock positions.

The patient's ophthalmologist has advised that a cataract extraction had been attempted many years ago and that fluid vitreous was lost at the time of incision. It was observed that the cataract was anterior polar in type. No specific details were recalled as the patient's record had been lost.

The patient was moderately hard of hearing and wore a hearing aid.

A-5

This 39-year-old, well-developed woman was darkly pigmented. For many years she had had frequent and severe occipital and frontal headaches, which were occasionally associated with blurred vision and colored halos about lights. This woman had been attended by many physicians, but had obtained no relief, and had finally resorted to naturopathy.

Ocular findings. The uncorrected visual acuity was 5/21 bilaterally; with correction 5/6—1 in the right eye and 5/4.5—3 in the left eye. The eyes varied from straight in the primary position to several degrees of alternating divergent strabismus. The extraocular movements were normal except for overaction of the right inferior oblique muscle when looking up to the left. A moderate lagophthalmos was present bilaterally due to the extensive exophthalmos which measured 24 mm. in the right eye and 21 mm. in the left eye (Hertel).[10]

Right eye. The corneal horizontal diameter was 13 mm. and 12.5 mm. vertically. The corneal stroma was clear except for a thin gray linear arcuate posterior surface deposit in the extreme periphery. This extended from the 4:30- to 7:30-o'clock positions. Despite the presence of a large, and very deep anterior chamber, there were numerous adhesions of the iris to the embryotoxon. The iris was a dark cocoa brown.

The pupil was large, oval horizontally, and displaced temporally. Ectropion uveae was noted about the entire circumference of the pupil. The sphincter was broad and easily observed. A small dehiscence existed in the iris running from the sphincter to the base at the 9:30-o'clock position. Other than for an occasional thin radial strand the iris stroma was absent. Transillumination indicated the atrophic character and moth-eaten appearance of the pigment layer. Although moderate iridodonesis was noted, there was no definite subluxation of the lens.

The lens and central media were normal. The optic-nerve disc was oval vertically, of pale color, and exhibited definite glaucomatous cupping. The retinal vessels, macular area, and periphery were normal. The intraocular pressure measured 15 mm. Hg (new Schiøtz). The confrontation field was markedly contracted in a concentric manner.

Left eye. The corneal diameter was 12.5 mm. horizontally and 13 mm. vertically. The corneal stroma was clear except for a gray linear streak

extending from the 12- to 5:30-o'clock positions in the extreme periphery.

The anterior chamber was large and deep. The pupil was displaced temporally and was flattened above and below. The iris sphincter was broad and prominent. The iris stroma was almost completely absent. Two minute dehiscences, each about 1 mm. in diameter, were located about 2 mm. apart at the 9-o'clock position. Numerous anterior synechias ran to the embryotoxon area.

The fundus appeared as in the right eye, except that there was only slight evidence of glaucomatous cupping of the optic nervehead. The tonometer tension was 14 mm. Hg (new Schiøtz). The confrontation field showed superior nasal contracture.

A-7

This asthenic, darkly-pigmented, 34-year-old woman presented nil vision in her right eye and was able to count fingers at one foot with her left eye. Her ophthalmologist reported that he had attempted to perform a visual iridectomy in the right eye but had been defeated when it became apparent that the corneal leukoma was adhered to the lens and iris. Poor vision and a pendular horizontal nystagmus had been present since birth. A diagnosis of bilateral otosclerosis had been made within the past four years. This woman was of good intellect and was a rather talented musician.

Ocular findings. There were 14 to 16 degrees of right divergent strabismus. The ocular mobility could not be studied because of lack of ocular fixation. A constant horizontal nystagmus of varying amplitude existed. No gross muscle paralysis was noted.

Right eye. The horizontal corneal diameter was 11.5 mm. and the vertical diameter was 11.8 mm. The central cornea exhibited a dense leukoma and the anterior corneal surface was quite flat. The peripheral or limbal cornea was opalescent.

The anterior-chamber details and a few iris details were demonstrated by transillumination. The anterior chamber was shallow but its depth varied greatly in the peripheral areas. The anterior ocular segment was large.

The pupil was placed at the 5-o'clock position, and a large peripheral iris dehiscence was present at the 10-o'clock position. The sclera over the anterior ciliary body was thin and revealed the underlying blue-black pigment of the latter.

The tonometer reading was 40 mm. Hg on first examination, but varied on subsequent readings from 25 to 45 mm. Hg (new Schiøtz).

Left eye. The corneal diameter was 11.5 mm. horizontally, and 11.2 mm. vertically. A large, irregular, dense central leukoma, measuring 3 by 4 mm., was present; the surface was flat and the substance of the scar showed conspicuous vascularity. Transillumination suggested an anterior capsular opacity upon which a pyramidal extension was superimposed. The latter did not seem to contact the cornea. The anterior chamber was moderately deep.

Gray linear posterior corneal surface deposits were noted, but no details could be obtained. The pupil was displaced temporally and appeared oval horizontally. An iris dehiscence was evident at the 5-o'clock position. The tonometer reading was 35 mm. Hg (new Schiøtz). The confrontation visual field was markedly contracted in a concentric manner.

A-10

This rather well-developed, light-complexioned young man, aged 27 years, declared that he was born with his corneal scars. He stated that he had had sufficient visual acuity to enable him to get about quite satisfactorily until the age of 18 years. The left eye was then injured in a gymnasium accident following which all vision was lost. This young man was quite talented and he was a piano tuner by trade.

Ocular findings. The visual acuity was nil bilaterally at the time of examination. There was eccentric bilateral wandering of the eyes associated with a coarse, irregular, but pendular, nystagmus. The eyes were divergent. No anomaly of the lids or conjunctivas was noted.

Right eye. The horizontal corneal diameter was difficult to measure due to scleral over-riding, but was 12 mm. or slightly less. A large irregular central leukoma was present. The surface of the cornea was flattened and quite vascular. The peripheral cornea was opalescent to transparent. The anterior chamber depth varied greatly but was quite shallow centrally and deeper at the periphery. Several gray linear deposits of embryotoxon were seen in the peripheral posterior corneal stroma. Anterior synechias were attached to the latter.

The pupil was displaced down and in at the 4:30-o'clock position. The sphincter could be easily observed. The lens seemed maturely cataractous. No iridodonesis could be exhibited. The anterior segment of the eye was large. The ciliary scleral area presented a light blue appearance. No staphyloma was present. The tonometer reading was 40 mm. Hg (new Schiøtz).

Left eye. The corneal diameter was 12 mm. horizontally and slightly less than 12 mm. vertically. There was scleral over-riding. The central cornea was densely leukomatous and was moderately vascularized. Transillumination indicated that the pupil was centrally placed. Many peripheral anterior synechias were present and accounted for the varying depth of the anterior chamber.

The anterior iris stroma was almost completely absent in certain areas and markedly attenuated elsewhere. Several small iris dehiscences existed; one at the 2-o'clock, another at the 2:30-o'clock, and a third at the 7-o'clock position. Embryotoxon extended from the 8- to 11-o'clock positions. Iridodonesis was present. The lens was maturely cataractous as viewed through the dehiscences of the iris. The tonometer reading was 28 mm. Hg (new Schiøtz).

F-1

This attractive, well-developed, dark-brown-haired, 29-year-old woman seemed surprised when informed that she was afflicted. Symptoms of increased intraocular pressure in either eye were stoutly denied. There was no evidence of von Recklinghausen's disease.

Ocular findings. The eyes were straight in the primary position, and the ocular movements were normal. The pupillary reflexes were present and equal in both eyes, but there was a sluggish reaction to direct light.

Right eye. The uncorrected visual acuity was 6/6—3. The corneal diameter was 12.5 mm. horizontally and 12 mm. vertically. The corneal stroma was clear except for a thin grayish strand on the posterior peripheral endothelial surface extending from the 2- to 7:30-o'clock positions. The anterior chamber was of moderate depth except inferiorly and temporally where it was shallow.

The pupil was displaced nasally and inferiorly. It was irregular and oval in shape and the pupil was adhered to the posterior corneal surface at the 5-o'clock position. Ectropion uveae was present at this point. The pupillary sphincter was markedly prominent due to the abscence of overlying stroma. The pigmented layer of the iris stood out in bold relief. Two small holes in the iris were present at the periphery in the 11-o'clock meridian. Iridodonesis was evident, but the position of the lens, if displaced, could not be determined.

The lens, central media, and optic-nerve disc were normal. The macular area, retinal vessels, and retinal periphery were devoid of pathologic changes. The confrontation visual field was normal. The tonometer reading was 12 mm. Hg (new Schiøtz).

Left eye. The uncorrected visual acuity was 6/15—1. The horizontal corneal diameter was 13 mm. The vertical diameter was 12.5 mm. The corneal stroma was clear except for a thin band of gray tissue on the posterior surface inferiorly and nasally. The anterior chamber was deep. The pupil was irregular and angular in outline and displaced nasally. The sphincter muscle was broad and prominent.

The iris stroma was nearly absent except for five delicate radial strands running from the base to the pupillary margin. No lesser arterial collarette could be seen. The pigment layer of the iris was intact but very atrophic as demonstrated by transillumination. The fundus appeared as in the right eye. The confrontation field was normal. The tonometer reading was 12 mm. Hg (new Schiøtz).

F-3

This well-developed, dark-brown-haired, alert young man, aged 24 years, reported that he had enjoyed a fair degree of visual acuity until 10 years of age. His relatives tell of a bilateral operation performed to relieve glaucoma at the age of three years. His vision had gradually deteriorated during the last decade until he became totally blind four years ago.

Right eye. The visual acuity was nil. The corneal horizontal diameter was 16 mm. The corneal stroma was clear. There was no evidence of rupture of Descemet's membrane. The anterior chamber was extraordinarily deep. The iris color was slate-black. The iris remnants were tremulous and were so atrophic that they seemingly lacked structure. There was no evidence of stroma and it appeared that only pigment remained.

A small band of iris extended across the visual axis and suggested a possible sphincter remnant. An extremely large iris dehiscence existed both above and below this strand. The superior coloboma probably represented the site of a former iridectomy.

The lens was maturely cataractous and was freely movable except for persistent zonular fibers inferiorly and nasally. The vitreous contained a large number of large and small strandlike opacities. The disc was very pale, very atrophic, and very deeply cupped.

The macular retinal area was mottled with pigment clumps and seemed moth-eaten. The entire retina was atrophic. The retinal vasculature was attenuated. The choroidal circulation was vividly seen. The tonometer reading was 46 mm. Hg (new Schiøtz).

Left eye. The horizontal corneal diameter was 14.8 mm. and the vertical diameter was slightly over 14 mm. A broad stripe of band keratitis extended across the cornea in the pupillary fissure area. *Clear* cornea was scant. The anterior chamber was very deep. There was considerable scleral over-riding. The sclera over the ciliary body had a light bluish tinge. The iris was very atrophic and the pigment appeared moth-eaten upon transillumination. A large iris dehiscence above represented presumably the area of surgical coloboma. The pupillary position could not be determined. The lens seemed cataractous and there was iridodonesis. The tonometer reading was 38 mm. Hg (new Schiøtz).

G-1

This well-developed, light-brown-haired, 30-year-old woman had had very large and prominent eyes since birth. She resembled A-2 in a great number of physical attributes. Since six years of age this individual had been totally deaf and an examination had revealed bilateral total nerve deafness. During the past five years recurrent severe ocular pain had been experienced in the left eye associated with marked loss of vision.

Ocular findings. The uncorrected visual acuity was 6/6–1 in the right eye and nil in the left eye. There were 20 degrees of right divergent strabismus (Priestly-Smith).

Right eye. The direct light and accommodation pupillary reflexes were prompt. The corneal horizontal and vertical diameter was 13 mm. The corneal stroma was clear except for a thin grayish-white posterior peripheral strand extending from the 6- to 10-o'clock positions. The anterior chamber

was deep. The pupil was displaced up and in. The sphincter muscle band was broad.

The iris stroma was thin and very attenuated, consisting of an occasional thin radial strand running to the pupillary margin. Ectropion uveae was present inferiorly and nasally. Numerous anterior synechias were present in the vicinity of the embryotoxon. The iris color was a soft golden brown. No iridodonesis was seen. The lens, central media, disc, vessels, periphery, and macular area were devoid of pathologic changes. The tonometer reading was 18 mm. Hg (new Schiøtz). The confrontation field was normal.

Left eye. The corneal horizontal diameter was 13.5 mm. and the vertical diameter was 13 mm. A moderate degree of scleral over-riding existed superiorly. The cornea was edematous. The anterior chamber was very deep. The pupil was dilated, oval vertically, and was fixed to all stimuli. The sphincter muscle band was broad and conspicuous. Ectropion of the uveal pigment existed inferiorly at the 6-o'clock position, the pigment being adhered to the endothelial surface of the iris.

Two minute iris dehiscences were present in the periphery at the 6-o'clock position, and several small holes were also present at the 10-o'clock position. The iris stroma was nearly absent and even the pigmented leaf appeared moth-eaten to transillumination.

After instilling glycerin, the funduscopic examination revealed that the lens and central media were normal. The optic-nerve disc was pale and very deeply cupped. There was extensive peripapillary retinal atrophy. The macular area was atrophic and the pigment mottled and finely clumped. The retinal vessels were small. The choroidal vasculature was prominent. The tonometer reading was 40 mm. Hg (new Schiøtz).

G-3

Very little definite information could be obtained in respect to this boy. He died early of a congenital heart lesion. It is known that he was afflicted, having had the large prominent eyes which are typical of this family. The late Dr. Kniskern of Muskegon, Michigan, could recall that the right eye possessed a horizontal slitlike pupil. The diagram was made up from this physician's description. A small dehiscence existed in the periphery in the 3-o'clock meridian, extending to the base. The visual acuity was less than 6/30 in the right eye and better than 6/9 in the left eye. The tonometer reading was not recalled. The iris sphincter was conspicuous and broad. The iris was of a dark brown color.

G-4

This child died of diphtherial complications at a very early age. The mother states that her eyes were involved. The eyes were large and prominent. The iris color was dark chocolate brown. No iris details were recalled.

G-5

This tall, thin, asthenic, blond young man was first seen at the university ophthalmic clinic, November 27, 1940. The history suggested that the patient had never experienced any ocular pain but that a gradual loss of visual acuity had been noted bilaterally for the past 4 years. During the last year the right eye had started to diverge and colored halos about lights had been encountered on occasion. Prior to his hospital visit he had desired no medical attention.

Ocular findings. There were 20 degrees of right divergent strabismus (Priestly-Smith). The ocular mobility was normal.

Right eye. The horizontal corneal diameter was 13 mm. and the vertical diameter was 12.5 mm. The corneal stroma was clear. The anterior chamber was deep. The pupil was dilated 8 mm. and was oval horizontally. The pupil reacted sluggishly to direct light and accommodation, but promptly to consensual light from the left eye. The pupillary sphincter was raised and broad.

The iris stroma was very attenuated but a sufficient amount was present to give the iris a blue color. No iridodonesis was present. The lens and central media were normal. The optic-nerve disc was pale and presented extreme cupping. Rather extensive circumpapillary retinal atrophy was present.

The macular area was stippled with minute clumps of pigment. The retinal vessels were normal. The retinal periphery was negative. The tonometer reading was 36 mm. Hg (new Schiøtz). A light field disclosed marked concentric field contracture.

Left eye. The corneal horizontal diameter was 13 mm. The corneal stroma was clear. The anterior chamber was deep. The pupillary sphincter was easily seen due to the atrophic character of the iris stroma. The pupil was oval horizontally and dilated 4 mm. It reacted promptly to all stimuli. No lesser arterial collarette was seen. The iris color was blue. The lens and central media were normal. The pulsation of the vessels on the disc surface and the cupping of the latter suggested increased intraocular pressure. The remainder of the fundus was devoid of pathologic changes. The tonometer reading was 60 mm. Hg (new Schiøtz).

Interval history (November 27, 1940, through May 13, 1941). Intensive miotics seemed to influence the intraocular pressure but very little. An Elliot trephination was performed once in the right eye and three times in the left eye. Cyclodialysis was also employed in the left eye. When discharged on May 13, 1941, the visual acuity was light perception in the right eye, and 6/6−2 in the left eye with the following correction: −0.50D. sph. $\circ$ +1.25D. cyl. ax. 167° = 6/6−2.

The visual field was contracted centrally to 20 degrees. The tonometer reading was 22 mm. Hg (new Schiøtz). The patient was not contacted again until 1944 when the following findings were noted:

Right eye. Visual acuity tests showed light perception inferiorly and temporally. The old trephination area above presented no bleb. The anterior chamber was deep. The pupil was very widely dilated and oval horizontally. The sphincter was broad and prominent. No essential change had occurred in the iris stroma. The iris was tremulous. A peripheral surgical iris coloboma was present at the 12-o'clock position. Anterior synechias were noted at the 9- to 11-o'clock positions. No changes were apparent in the fundus. The tonometer reading was 30 mm. Hg (new Schiøtz).

Left eye. The corneal scleral junction showed the three trephination bleb areas all quite flat and scarred down. The cornea was clear. The anterior chamber was deep. The pupil was displaced down and out and was slightly dilated. Three peripheral surgical colobomas were seen at the 11-, 12:30-, and 2-o'clock positions. The iris stroma was less blue than on the original examination, as the brown ectodermal pigment was now more conspicuous. Anterior synechias were seen from the 2- to 5-o'clock positions, but no embryotoxon was apparent.

Funduscopically the lens was clear and the central media were negative except for vitreous opacities. The disc was markedly atrophic and cupped, and the retina showed no change. The tonometer reading was 16 mm. Hg (new Schiøtz).

G-9

This 20-year-old young woman of asthenic build was first seen at the university ophthalmic clinic, November 8, 1932, her chief complaint being severe frontal headaches.

Ocular findings. The eyes varied from straight to several degrees of left divergent strabismus. The ocular movements were normal.

Right eye. The corneal diameter was 14 mm. horizontally, and 15 mm. vertically. The corneal stroma was clear except for embryotoxon extending from the 9- to 12:30-o'clock positions. The anterior chamber was deep. The pupil was displaced up and in toward the 11-o'clock position but reacted to direct light, consensual light, and accommodation stimuli. The pupillary opening was irregular in shape, being somewhat cuboidal. Ectropion uveae was present at the 11-o'clock position. The iris was very atrophic in the lower inner two thirds. A large vertical dehiscence extended from the sphincter border to the iris base at the 5-o'clock position. The sphincter pupillae was prominently seen.

The slitlamp revealed some vascularization of the iris surface. A persistent embryotoxon membrane strand extended from the 5- to 2-o'clock positions. The corneal radius was 9.1 mm. The lens was dislocated slightly up and out. A small Mittendorfer was present nasally. The central media were normal. The disc was small and presented moderate, but early, atrophy and cupping. A large cilioretinal vessel was seen at the 11-o'clock position. The remainder of the fundus was negative.

Left eye. The corneal diameter was 13 mm.

horizontally and 14 mm. vertically. The radius of curvature was not determined because of irregular astigmatism. The cornea was irregular in outline as a result of scleral over-riding. A large moderately well-vascularized leukoma occupied the central zone of the cornea. The entire cornea showed deep or interstitial vascularization. The anterior chamber was deep.

A large triangular dehiscence was present in the iris, the apex being at the 1-o'clock position and the base extending from the 5- to 7-o'clock positions. Through this large dehiscence the ciliary body and attenuated zonular fibers could be easily seen with the slitlamp. A small anterior capsular opacity was present just above the anterior lens pole. A distinct bluish-white posterior corneal deposit ran around the nearly complete peripheral circumference. The lens was displaced slightly up and in. Otherwise, the lens, central media, and fundus appeared as in the right eye. The tonometer reading was 65 mm. Hg (new Schiøtz).

Interval history (November 18, 1932, to September 26, 1945). During this interval two Elliot trephining operations were performed in the right eye and three in the left, combined with a Lagrange sclerectomy in order to control the intraocular pressure. The left eye finally became phthisical. The visual acuity in the right eye remained 6/20—1 up to the above date. The tonometer reading on November 26, 1945, was 40 mm. Hg in the right eye. Iridencleisis was advised but refused by the patient.

Last examination (February 25, 1946). The patient had observed complete loss of vision three days prior to consultation, but vision gradually returned to the point where she could count fingers on February 25, 1946. The corneal horizontal diameter was 14 mm. There was moderate scleral over-riding superiorly. The corneal stroma was clear except for embryotoxon superiorly and temporally. In this region the iris and sphincter muscles were included in a broad anterior synechia.

There was no evidence of previous trephinations except for a small iridectomy at the 2-o'clock position. The dehiscence below was larger than when previously seen. The iris was tremulous and the lens was dislocated down and in. A small coloboma or notch of the lens was present at the 11:30-o'clock position.

Right eye. The lens showed nearly complete opacification superiorly, but was fairly clear inferiorly. No other fundus changes were seen. The tension was 45 mm. Hg. An iridencleisis was advised and performed by a local ophthalmologist, but the operative result has not yet been ascertained.

Gonioscopy (February 25, 1946). The angle was well seen and seemed completely filled with a grayish-golden trabecular tissue, which was decidely more dense in certain areas, especially superiorly and temporally. The ciliary processes were seen through the small iridectomy at the 12-o'clock position. The iris surface was adhered to the cornea from the 11:30- to 12-o'clock positions, at which place the sphincter was included in the em-

bryotoxon. Some fairly well-dilated vessels were seen in among the abnormal meshwork. Schwabe's line could not be visualized, and, indeed, no normal anatomic details of the angle were noted.

G-11

This well-developed, intelligent and coöperative little 4-year-old girl presented the most unusual ocular changes seen in her sibship. Her eyes had not changed since birth and she had never had previous ophthalmologic examination.

Ocular findings. The eyes were straight in the primary position, with considerable divergence noted under cover.

Right eye. The uncorrected visual acuity on the E chart was 6/15+. The corneal horizontal diameter was 12.5 mm. and the vertical diameter was 13 mm. The cornea was clear except for an embryotoxon present from the 11- to 7-o'clock positions. The anterior chamber was very deep.

The pupillary opening was a horizontal slit, 5 to 6 mm. in length, running obliquely from the 10- to 3:30-o'clock positions. The nasal portion of the pupillary opening was adhered to the embryotoxon. A dense band of ectropion uveae was also adhered to the latter. The sphincter muscle was broad and very conspicuous due to the attenuated character of the iris stroma. The latter was represented by thin incomplete grayish radial strands. No iris collarette was seen. The pupil showed normal direct, consensual, and accommodative reflexes.

The iris color was a grayish brown. A small dehiscence, 1.5 mm. in length, was present in the atrophic iris at the 10-o'clock position near the iris base. Some vascularization was evident on the iris surface. The iris was tremulous. No ectopia lentis was noted.

The lens and central media were clear. The disc was oval vertically, of excellent color. A moderate-sized physiologic depression was present. The vessels, macular area, and retinal periphery were devoid of pathologic changes. The fundus was easily seen with a plus-one sphere. The tonometer reading was 21 mm. Hg (new Schiøtz).

Left eye. The visual acuity was 6/15+1 as determined by the E chart. The corneal horizontal and vertical diameter was 12.5 mm. The corneal stroma was clear. A small thin grayish band of tissue was present on the posterior corneal surface in the extreme periphery and extended from the 11- to 2-o'clock positions. The anterior chamber was quite deep.

The iris was grayish brown in color. The superficial stroma was nearly absent except for attenuated radial strands, as noted in the right iris. The sphincter band faded out into the substance of the pigmented leaf of the iris. The pupil was irregular and somewhat triangular, with the base situated inferiorly and nasally. The pupil was displaced up and out. Minimal ectropion uveae was noted at the 6-o'clock position. The iris was tremulous. Funduscopically, the left eye presented normal findings as in the right eye. The tonometer reading was 23 mm. Hg (new Schiøtz).

ETIOLOGY

It is rather obvious that the ocular defects in this family are germinal in origin and are inherited in a dominant pattern. It is possible, therefore, to avoid a discussion of maternal influences and environmental noxious agents of unknown character and effect. The factor to be discussed is that of the mechanism at work, and, if possible, to implicate the ocular tissue primarily involved. The diversity of ocular pathologic changes is so varied and extensive that the discussion cannot be limited to one anomaly but must be inclusive of influences affecting the entire anterior ocular segment.

There are available in the literature numerous explanations or theories attempting to explain similar developmental or congenital anomalies of the anterior ocular chamber, cornea, and iris. Most writers seem to look with favor on the following two hypotheses:

I. A failure of development of the neural ectoderm especially with reference to a primary failure of the development of the rim of the optic vesicle.[9]

II. A mechanical obstruction to the development of the iris and anterior-chamber angle by persisting remnants of the tunica vasculosa lentis (capsulopupillary fibers) and its anastomoses with the extraocular mesoderm.[10]

Theory I anticipates an association of other ectodermal defects such as congenital amblyopia, retinal anomalies, nystagmus, lens-ciliary processes, and zonular defects. In this family A-7 and A-10 presented nystagmus, and F-3, G-9, and G-11 disclosed moderate ectopia lentis in association with extensive iris and corneal changes. No demonstrable posterior-segment ectodermal changes were recorded.

Theory II suggests that there is an abnormal prolonged persistence of the vascular network around the margin of the optic cup. In the anterior segment, this would offer an obstacle to the subsequent development of the iris and ciliary processes. When

such exists early and in extensive degree, aniridia may result; if only a partial obstruction exists, a coloboma of the iris may develop; or if very mild in extent and quite late, an ectopic pupil may ensue. It would be entirely possible to explain the majority of the pathologic changes of the affected eyes in this pedigree by postulating variations of this second theory.

A third and somewhat related theory is suggested by the findings of Hagedoorn (1928) who reported evidence that the anterior chamber is formed by the laying down of a scaffolding in the anterior vitreous (ectodermal) of a primitive cornea, anteriorly, and a primitive membrane, posteriorly, both of which are later permeated by invading mesoderm. Anomaly in this primary ectodermal scaffold could explain the later mesodermal defects effecting congenital corneal leukomas (A-7, A-10); embryotoxon and peripheral anterior synechias (C-1, A-2, A-7, A-10, F-1, G-1, G-9, and G-11); and the persistent embryonic tissue in the filtration angle in G-9 and G-5.

In this family and in those reported in the medical literature it is possible to select individuals whose defects could be explained by either theory. When such is the case, one anticipates that many influences are playing a role or that some entirely unsuspected and unknown mechanism is at work.

The embryologist is prone to stress the time relationship and sequence of events occurring in the development of the organism. He is aware that certain features of development occur only at and during a specific limited period of time.

It is also important to note that developmental phenomena occur in direct and quite meticulous sequence to preceding events. Much has been learned in respect to the influence of noxious chemical agents on the embryo with reference to the aforementioned time relationships.

It has been observed that the chemical action of certain agents will affect most of

those structures that are changing (growth) extensively and rapidly at the time of influence.

The same agent working at a different time will produce totally different effects depending again on which structure or tissue is undergoing the most energetic metabolism at the moment. Thus the cells exhibiting the greatest metabolic activity at the specific time that a noxious agent is present will demonstrate the most marked changes.

It is interesting to note that the geneticist emphasizes that genes are merely chemical agents and thus certain mutant genes can be expected to exert a relatively abnormal chemical or noxious effect on the developing embryo. In this light the tissue most active in its metabolism at the time that the gene exerts its effect would suffer according to the extent and duration of that influence.

In this family one could postulate an early and prolonged effect in A-7 and A-10 starting at the 6- to 9-mm. stage, thus effecting the extensive corneal and anterior chamber changes. The surface ectoderm and primary vitreous are most actively changing at this stage. The nystagmus present in both individuals could also suggest a deleterious influence on the neuro-ectoderm present as the primary optic vesicle at that stage.

In summary, one is forced to say that the specific mechanism producing the reported ocular anomalies is unknown. That a germinal influence is present cannot be denied in that the trait is transmitted in a very definite dominant pattern of inheritance.

TREATMENT

The glaucoma which accompanies the anterior-chamber anomalies described in this report has proved to be most difficult to manage either medically or surgically. Miotic therapy has had little, if any, influence upon the intraocular pressure in those individuals studied at the university ophthalmic clinic (E-1, A-7, G-5, and G-9).

Surgery, consisting of iridencleisis, iridectomy, trephine sclerotomy, and cyclodi-

alysis, has failed completely in those cases so treated. Extensive scar-tissue reaction has been a constant finding in those eyes which were reoperated and such connective-tissue proliferation could account for the failure of most of the surgical procedures employed. Iridencleisis is apparently controlling the tension in the right eye of G-9, but the period of observation has been very short.

Goniotomy has been suggested by its advocates for use in such cases as are encountered in this kindred. We have not utilized this procedure in this family but do anticipate doing so if granted the opportunity.

While not intending to discourage the quest for better methods of repairing such abnormalities, we would urge that the control of such defects should preferably be prophylactic. We have advised the affected members of these families of the genetic pattern of transmission and have strongly impressed them with the consequences of further propagation.

ECONOMIC CONSIDERATIONS

In general, the level of intelligence of the members of this family was moderate to good with no outstanding variation in any sibship. The occupation of most wage earners was clerkship and unskilled labor. The homes of most were modest but in a few the conditions were poor. The personalities of most individuals were affable to pleasant once a rapport was established.

An interesting and gratifying observation was the degree of independence and self-reliance exhibited by those individuals educated at the Lansing School for Blind (A-7, A-10, F-3, and A-4) all of whom were capable of earning their own living or managing their own household. F-3 and A-10 drew good salaries during the war as factory workers.

The marriage of A-7 to a classmate from the school for blind is disquieting. They do not intended to have children but no reliable

steps to prevent this likelihood have been taken to date.

Despite the position of the families, a considerable financial burden has been imposed on the county and state welfare by this family. The expense of support of the totally blind C-1, G-5, and F-3 has not been insignificant. The cost of special education has been high. The affected members have also been, in a few specific cases, a burden financially and in personal care to their siblings and parents. A-4, A-7, F-3, A-1, G-9, and G-5 have been frequent visitors to ophthalmologists and semiprofessionals. Such attention has resulted in the expenditure of many thousands of dollars in surgical and medical fees. If only C-1 had been prevailed upon not to have had children!

CONCLUSIONS*

1. A pedigree presenting the dominant inheritance of a trait effecting a wide variety of anterior ocular segment anomalies has been reported.

2. The ocular anomalies adversely affect the physical and mental well being, as well as the economic and educational achievements of the majority of the affected.

3. The associated glaucoma is most difficult to manage either medically or surgically.

4. Primary importance has been attached to giving eugenic advice to all members of this kindred.

University Hospital.

* For discussion, please see page 58.

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THREE CASES OF MARCUS GUNN PHENOMENON IN TWO GENERATIONS*

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HEREDITARY MARCUS GUNN PHENOMENON

The hereditary aspect of the Marcus Gunn phenomenon has received but scant attention from medical observers. The medical literature in this respect is indeed quite sterile. It is the purpose of the authors to present herein a family in which the Marcus Gunn anomaly occurs in three individuals in two consecutive generations.

I. GENERAL LITERATURE

The ill-termed "jaw-winking" phenomenon, in which there is an associated involuntary movement of one or both upper eyelids with movements of the lower jaw, was first described in 1883 by Marcus Gunn.[1] The association of extraocular muscle palsy with the phenomenon was emphasized by Lutz,[2] in 1919. Other observers have included such associations as: movements of the eye lids upon blowing out the cheeks, swallowing, singing, speaking, chewing, sucking, and thrusting out the tongue.

Several very excellent reviews are available for study and include reports by W. W. Sinclair,[3] in 1895; A. Lutz, in 1919; H. Villard,[4] in 1925; and F. C. Grant,[5] in 1936. The latter summarized 101 cases up to 1935. Among Grant's observations were: (1) Males are more frequently affected; (2) the left eyelid is the more commonly implicated; (3) the absence of ptosis of both eyelids has occurred only seven times;

and (4) bilateral ptosis has been noted in only three cases.

W. W. Sinclair summarized 32 cases and divided them into four variations (Series I) of the phenomenon as follows:

I. (13 cases) of unilateral congenital ptosis in which the drooping eyelid is raised both when the mouth is opened (? digastric muscle) and also when the jaw is directed to the opposite side (external pterygoid muscle).

II. (13 cases) of unilateral congenital ptosis in which the drooping eyelid is raised when the jaw is depressed but is not raised on lateral movements of the jaw.

III. (3 cases) of unilateral congenital ptosis in which the drooping eyelid is raised with lateral movement of the jaw (action of the external pterygoid muscle) but not with simple opening of the mouth.

IV. (4 cases) in which similar associated movement of one upper eyelid with movements of the lower jaw occurs but in which there is no ptosis.

W. W. Sinclair's classification included two other series: (1) Acquired pseudo-Graefe phenomenon and (2) Duane's retraction syndrome. These have been disregarded since attention is being confined wholly to the congenital type in our studies.

ETIOLOGY

The etiology of the syndrome has stimulated much literature as well as research, but unfortunately a satisfactory explanation is yet lacking. Helfreich and Bernhard[6] emphasized neuronal intercommunications between the nuclei of the facial, trigeminal, and oculomotor nerves. Bing[7] suggested a cortical or subcortical pattern analogous with the Bell's phenomenon.

Lewy, Grant, and Groff[8] believed that the

Marcus Gunn phenomenon could be explained by the presence of a proprioceptive arc, the afferent limb (in part) being the sensory division of the mandibular division of the trigeminal nerve. The efferent limb to the eyelid they assumed to be by the autonomic fibers questionably via the ophthalmic division of the trigeminal nerve.

Spaeth[9] wonders "if the Marcus Gunn syndrome cannot be caused by congenital misdirection of developing peripheral nerve fibers; the source of the fibers arising properly in the proper nuclei, the faulty distribution, however, occurring in the posterior longitudinal bundle or even more peripherally within the brain stem, excluding wholly any relationship of the autonomic nervous system."

The incidence is rather rare, there being now available in the literature only about 110 to 115 cases. Spaeth estimates that when properly observed 2 percent of all cases of ptosis would demonstrate the Marcus Gunn phenomenon. We feel this to be a little high but do agree that, if looked for, the incidence will be rather higher than heretofore anticipated.

II. DISCUSSION OF HEREDITARY CASES REPORTED IN THE LITERATURE

There have been several instances of familial occurrence of the Marcus Gunn anomaly reported in the literature. Leri and Weill[10] reported bilateral Marcus Gunn phenomenon in a woman, aged 63 years, and congenital unilateral Marcus Gunn anomaly in her son, aged 49 years. There were no other similarly affected individuals in the family.

Volmer[11] reported a family in which there were six members (hearsay evidence) with the jaw-winking anomaly, three females and three males in four generations, one generation being skipped, the defect being transmitted through two supposedly normal males to the succeeding generation. Volmer only examined one of the affected individuals, an

8-year-old girl with unilateral left-lid involvement.

Meyer[12] reported the phenomenon in a father and his 3-year-old daughter. In the latter it was congenital, left sided, and produced by eating and drinking. Blok[13] observed the phenomenon in two brothers. Phillips[14] also reported the Marcus Gunn phenomenon in two brothers, aged 3 years and 7 years.

There are also several papers in which the Marcus Gunn anomaly was known or thought to be present in other members of the family. E. C. Fischer[15] reported a case involving the right eyelid of a male child and stated that the right eyelid of the child's grandfather had had a similar appearance.

Jean S. Charamis[16] wrote that the brother and father of his patient (male) had had a similar ptosis but that he was unable to see or examine either. Vossius[17] mentioned the association of external ophthalmoplegia with his case of jaw winking and emphasized that a brother of his patient also had external ophthalmoplegia but no Marcus Gunn effect. E. Cooper[18] quoted family remarks in his case to the effect that an aunt had had a "similar eyelid."

PEDIGREE

The study of the family described here (fig. 1) was first undertaken because of the interest stimulated by the occurrence of this rather rare human anomaly in several members within two generations. The family is largely of farmer stock residing in southeastern Michigan. The propositus and his mother were referred for consultation to one of us (H. F. F.) through the courtesy of Dr. Thomas McEachern of Ann Arbor, Michigan. The pedigree chart is of the conventional type. Siblings are arranged horizontally and in order of their birth. Each generation is indicated by a Roman numeral and each member of the family proper by an Arabic numeral. Combination of these numbers are used to identify persons in the text.

PATHOLOGIC NOTES

(III-1). The propositus, a boy aged 7 years, exhibited the Marcus Gunn phenomenon in the left eye only. This jaw winking was first observed in the child as a nursling and was described by the mother as having been more conspicuous then than it was when first examined by us.

The visual acuity (uncorrected) was: O.D., 6/9+2; O.S., 6/6−2, E chart. Muscle

in both eyes. The funduscopic examination was negative in both eyes.

There was a definite retraction of the upper eyelid, O.S., associated with chewing movement of the jaw. This was accentuated when the jaw opened and when it was protruded. Applying forceful resistance against the jaw accentuated the degree of elevation of the lid which was at the most only moderate, measuring 2 to 2.5 mm. Down-
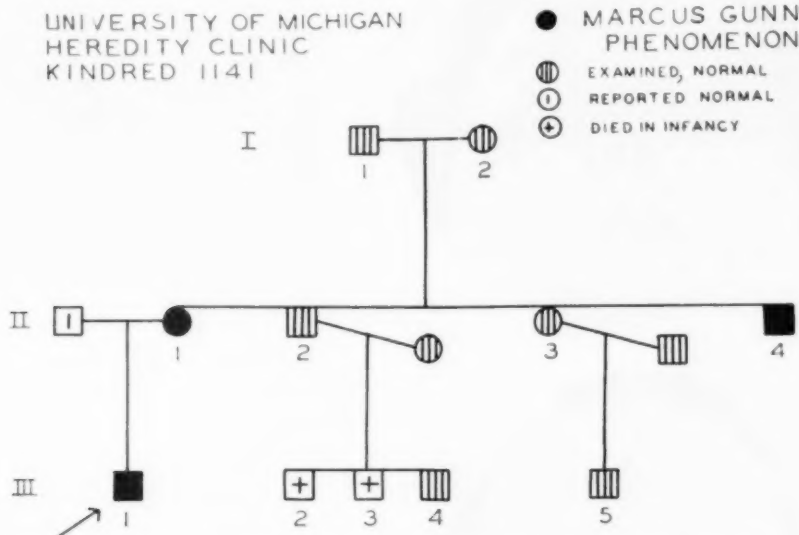
Fig. 1 (Falls, Kruse, and Cotterman). Pedigree chart showing occurrence of Marcus Gunn phenomenon in two generations of a family.

measurements were 2-degrees esophoria for distance and orthophoric in accommodation.

The eyes were straight in the primary position with minimal lateral deviation under cover. The external ocular movements were normal. The p.c.b. was 60 mm. The upper eyelids were normal and presented a good lid fold bilaterally. There was a very slight ptosis in the left eye, the palpebral fissure measuring 8 mm. O.D., and 7.5 to 7 mm., O.S. The pupils were normal. The pupillary reflexes were likewise normal. Conjunctiva, cornea, and anterior chamber were normal

ward gaze made the lid retraction more evident. The lids could be elevated voluntarily. Very minimal or no upward movement of the lid was produced by deviating the jaw to the right. No other associated cranial nerve action produced the retraction of the lids.

(II-1). This 31-year-old, well-developed woman accompanied her son for examination. Like her child her anomaly had been first noted when she was a baby and especially when she was nursing. Her facial appearance was pleasing and a right ptosis

could be noted only on careful observation. Chewing and talking produced observable retraction of the right upper lid.

The visual acuity was: O.D. 6/6−1; O.S., 6/6−3. The near point of accommoda-

position with minimal lateral deviation under cover. The extraocular movements were normal. The conjunctiva, cornea, anterior chamber, and iris were negative. The pupils were equal and round. The palpebral fissure,

Fig. 2 (Falls, Kruse, and Cotterman). Three individuals in two generations exhibiting the Marcus Gunn phenomenon. (Kindred 1141, Heredity Clinic, University of Michigan.)

tion was J0 at 18 cm., O.D., and J0 at 17 cm., O.S. Muscle measurements revealed orthophoria in distance and 3 degrees of exophoria in accommodation. The p.c.b. was 75 mm.

The eyes were straight in the primary

O.D., measured vertically 8 mm. and O.S., 8.5 mm. The funduscopic examination was normal in both eyes. There was a definite retraction of 2 to 2.5 mm. of the right upper eyelid, more marked with protrusion of the lower jaw. Little or no elevation of the

upper right eyelid could be noted with lateral movements of the jaw to either side. Downward gaze of the eyes accentuated the retraction movement. No other cranial nerve association could be demonstrated.

(II-4). This well-developed, muscular 28-year-old man was not conscious of his Marcus Gunn phenomenon until our examination revealed its presence. The visual acuity was: O.D., 6/6; O.S., 6/9−2.

The external examination disclosed that the eyes were straight in the primary position with moderate lateral deviation under cover. The lids were normal with a good lid fold of both upper eyelids. A barely perceptible ptosis, O.D., was noted. Palpebral fissure vertical height was 8.5 mm., O.D., and 9 to 9.5 mm., O.S. There was gross nystagmoid jerking in the extremes of lateral gaze in both eyes. The conjunctiva, cornea, anterior chamber, and iris were normal in both eyes. The p.c.b. was 105 mm. The funduscopic examination was normal in both eyes.

On protruding the mandible, the upper right eyelid elevated approximately 2 to 3 mm. and remained elevated until the jaw was retracted. The eyelid moved synchronously with the back and forth action of the jaw. Slight retraction of the upper right eyelid was noted on ordinary chewing. Neither lid was seen to move on lateral movement of the mandible. There were no other cranial nerve associations demonstrable.

No other member of the family displayed any suggestion of the phenomenon.

HEREDITY OF THE PHENOMENON

All of the available evidence including the family herein reported and a second now being studied suggests that the trait is most probably inherited as an irregular dominant. In such a pattern many deviations may occur from the anticipated ratios. Usually when a trait is dominantly inherited one may expect certain rather clear-cut patterns of events, such as:

1. An affected individual will have an affected parent.

2. Fifty percent of the affected individuals' children may be anticipated to be likewise affected.

3. The trait does not skip a generation, but is dramatically constant from generation to generation.

In an irregular dominant pattern of inheritance certain unknown factors (modifying genes) may exert an influence on the presence or absence of the anomaly. The gene may be present in the germ-plasm of an individual (genotype) but may not be evident physically (phenotype). This latter individual may, however, transmit the trait to his or her children who can present the typical phenotypic appearance of the phenomenon. The degree of severity of the manifestation may vary greatly within the same family, from unilateral severe ptosis to very mild bilateral Marcus Gunn phenomenon without ptosis (variable expressivity), or no observable abnormality at all. Studies now in progress will be presented soon to support the latter observation.

COMMENT

The necessity for a careful and meticulous observation of every available member of families having the Marcus Gunn phenomenon cannot be too thoroughly emphasized. II-4 did not know he had the phenomenon, nor did his relatives, and certainly we would have missed him if we had relied merely on hearsay evidence.

SUMMARY

1. A family demonstrating a possible irregular dominant inheritance pattern of the Marcus Gunn phenomenon is presented.

2. Literature is presented to support the hereditary aspect of the Marcus Gunn phenomenon.

3. A plea is made for meticulous study of all members of Marcus Gunn families.

University Hospital.

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DISCUSSION

A GENE PRODUCING EYE DEFECTS AND MARCUS GUNN PHENOMENON

Dr. CLEMENT McCULLOCH (Toronto, Canada): Dr. Falls has presented theories in his first paper to explain multiple anomalies on the basis of one characteristic in one chromosome. I am wondering if there is any evidence in the distribution of cases in the family to suggest the presence of multiple characteristics in one chromosome?

Secondly, in discussing the family presented in the first paper he mentioned horizontally oblique discs in at least one case. I was wondering if he noticed oblique discs aside from the glaucoma change in any great number of that family and if they followed the anomaly of the anterior segment of the eye?

Dr. K. W. ASCHER (Cincinnati, Ohio): Dr. Fall's contribution is certainly important and stimulating. The following approach might help to explain the congenital Marcus Gunn phenomena as well as those which appear during the adult life. Connections between the oculomotor and other nuclei are an atavistic inheritance, and associated movements occur in animals and in children like the forced opening of the mouth associated with opening of the lids.

While these connections always are pres-

ent their utilization is inhibited during normal adult life. This inhibition may be missing either congenitally, as in the great majority of the Marcus Gunn phenomena, or it may disappear temporarily as in a case described by me in 1937 (Med. Klin., 33:1259).

A Marcus Gunn phenomenon appeared in a 44-year-old man during the recovery from a unilateral third-nerve paralysis. After intensive antiluetic treatment, the patient noticed that his upper lid, paralyzed for months previously, opened involuntarily as often as he performed chewing movements. This associated movement was observed for about a week and disappeared when the patient became able to open his eye voluntarily.

This is a single observation only but together with phylogenetic and ontogenetic analogies it seems to indicate that the Marcus Gunn phenomenon might be due to disinhibition of a normally inhibited, preformed, associated innervational mechanism.

DR. DAVID G. COGAN (Boston, Massachusetts) : A point of interest, although I don't know whether it has any significance, is that this lid retraction occurs only during the opening act of the jaw. If the jaw is held open, the lid does not stay retracted. I have no explanation for it. Maybe Dr. Falls has made a similar observation or may have some explanation.

DR. FALLS (closing) : First, in respect to Dr. McCulloch's question—that is, "Is there any evidence of the fact that the multiple characteristics in this family may be due to multiple genes?"—I should like to say that it is very difficult to study multiple gene effects in human genetics, but because the pedigree in this family presents such a definite inheritance pattern, mainly that of dominant inheritance, and because the gene effect is so limited to the anterior chamber, we felt that we were dealing with a uni-gene factor.

In respect to multiple changes in the body due to one gene a rather interesting study by Dr. Cotterman, at our clinic, indicates a single gene will produce a specific defect in the developing embryo and in turn produce tremendous changes in the entire body due to the influence of migrating blebs of cerebral spinal fluid.

I am not too sure, Dr. McCulloch, whether you meant slit pupils or oblique discs.

DR. McCULLOCH : Oblique discs.

DR. FALLS : There were no frequent abnormalities of the optic nervehead in this family. It is my opinion that the oblique disc mentioned was only a chance association.

I should like to answer Dr. Ascher and thank him for his contribution. I cannot add anything to his statement. I do want to emphasize, however, that we limited our study entirely to the jaw-winking phenomenon of congenital origin. It is my opinion that your case report comes largely under the role of pseudo-von Graefe phenomenon.

In respect to Dr. Cogan's contribution I wish to mention that I have a more interesting family which will soon be published in which there are two specifically different types of Marcus Gunn phenomenon present. One member of the family presents no ptosis whatsoever, but when this man opens his jaw and turns it to the right and then to the left he has an elevation of the opposite lid. His sister has a unilateral ptosis and again there is lid elevation upon lateral movements of the jaw. It is true that the lid retraction does gradually relax with continuation of the jaw protrusion. I do not believe that I can explain this phenomenon.

In closing I should like to urge that the families in which Marcus Gunn phenomenon occur be more thoroughly studied, particularly from the viewpoint of the inheritance of the anomaly.

ELECTROCOAGULATION OF THE SCLERA*

REDUCTION IN OCULAR VOLUME AND PATHOLOGIC CHANGES PRODUCED

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I. INTRODUCTION

Although the value of sealing retinal holes in the cure of retinal detachment, pointed out by Gonin,[1-5] (1921-1930), has been confirmed by most subsequent workers in the field of retinal detachment surgery, a significant percentage of surgical failures continues to occur. Numerous techniques and almost every conceivable type of instrument have been employed to seal retinal holes. It therefore seems reasonable to investigate further any supplementary aids which are available to help reduce the number of failures. One of these aids is scleral resection or scleral shortening.

Reduction in volume of the scleral coat by resection was introduced in 1903 by Leopold Müller.[6] Müller mentioned its use in 7 instances all with satisfactory results. His stated aim was to reduce the volume of the sclera to that of its contents. Various reports have since appeared in the literature regarding the use of scleral resection. Müller,[7] 1930, reported results in 19 patients.

In 1934, Lindner[8] reported its use in retinal detachments carrying poor prognoses such as those associated with aphakic eyes, nystagmus, proliferating retinitis, and funnel-shaped detachments with bands following previous retinal detachment surgery. Lindner described his technique in detail.

He was very conservative in estimating his results and advocated doing the procedure only after electrocoagulation had previously been done. Pischel,[9] Borley,[10] Vail,[11] and Bogart[12] have written recently on the subject in our own country. Vail pointed out its value in retinal detachment with equatorial staphyloma.

Shortening of the eyeball or reduction in volume of the sclera has been accomplished by excising a piece of sclera. This can be a technically difficult procedure. There is reason to believe that some reduction in ocular volume can also be produced by electrocoagulation. Albaugh and Dunphy,[13] 1942, first commented upon the marked initial rise in pressure associated with the cyclodiathermy operation. Stocker,[14] 1943, made the same observation. Meyer and Sternberg[15] claimed that the volume of the eyeball is decreased in cyclodiathermy operations because of shrinkage of the sclera. Berens, Pischel, and Thorpe, in discussing a paper by Pischel,[9] stated that electrocoagulation consistently produced rather marked shrinkage of the sclera during retinal detachment operations. One of us (H. G. S.) made similar observations independently which led to the work presented in this paper.

Little is known about the actual changes in volume associated with either electrocoagulation of the sclera or scleral resection. Such knowledge and a comparison of the changes in volume produced by either technique might be of some value. If reduction in ocular volume could be safely produced by electrocoagulation which was comparable in amount to that resulting from scleral resection, a much simpler method of approach might be made available for clinical use. The duration of such changes should also be as-

certained. The following experimental work was therefore performed.

II. PURPOSE OF EXPERIMENT

The object of the experiments about to be described was:

A. To measure the volume changes occurring in the eye as a result of electrocoagulation of the sclera.

B. To establish the duration of such changes in volume.

C. To compare the changes in volume resulting from electrocoagulation with those of experimental scleral resection.

D. To observe the pathologic changes occurring in eyes so coagulated.

III. TECHNIQUES AND APPARATUS

Several methods for measuring the volume of an eyeball and subsequent volume changes suggested themselves. After some trial, a fluid displacement method was decided upon and suitable apparatus devised (figs. 1 and 2). This consisted of a bell-

Fig. 2 (Scheie and Jerome). Device for volume measurement. (A) Etched mark indicating level to which device is filled. (B) Ground-glass surfaces on "bell" and base, lightly oiled. (C) Hooks, on which rubber banks from base are fastened. (D) Glass tube to fill device, with etched mark at zero level.

shaped chamber of 15-cc. capacity. The bell, which was open at the bottom, rested upon a base with a flat surface. Their approximating surfaces were of ground glass.

The dome of the bell was surmounted by a cannula that was etched at the level corresponding to 15 cc. when the apparatus was filled. At the center of the base was a small opening communicating with a small cannula which connected through a short piece of heavy rubber tubing to a 10-cc. analytical certified burette calibrated in 0.02-cc. divisions.

A fine film of oil applied to the ground glass surfaces achieved a water-tight union between the base and the bell. This union was given support by the traction of elastic bands.

The eye was debrided of its muscles and all adherent connective tissues and was placed on the center of the base and covered by the bell. Fluid was then allowed to enter the chamber filling it to the mark on the can-

Fig. 1 (Scheie and Jerome). Apparatus for volume measurement, assembled.
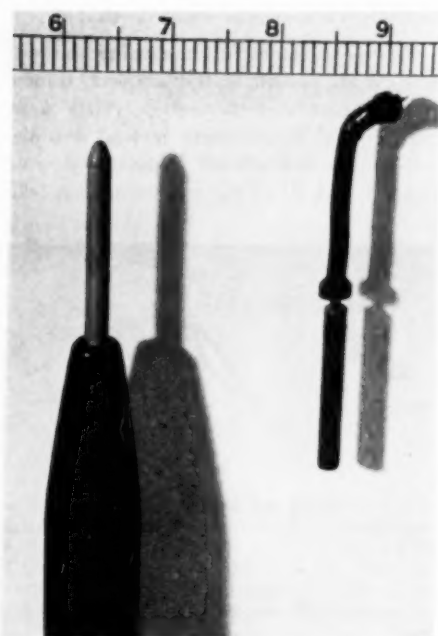
Fig. 3 (Scheie and Jerome). Surface and penetrating electrode employed in experiments.

nula surmounting the bell. The difference between the volume of fluid required to fill the apparatus containing the eye and the volume when empty gave the amount of fluid displaced by the eye, or its volume. Various control measurements were made.

Measurements repeated on the same eye could be duplicated with an average error of

0.01 cc. (Table 1). The eyes were kept at a constant intraocular pressure, for obviously an eye displaces less fluid when soft than when hard. To evaluate this relationship, measurements of five eyes were made with pressures varying from an eye too soft to measure with a Schiøtz tonometer* to 50 mm. Hg (Schiøtz) (Table 2).

The average difference between these two extremes of pressure was 0.48 cc. The difference between 10 mm. Hg and 25 mm. Hg was only 0.02 cc. while that between 25 mm. Hg and 50 mm. Hg (Schiøtz) was 0.1 cc. All volume measurements were subsequently done in these experiments on eyes in which the intraocular pressure was maintained between 15 and 25 mm. Hg because of the small error at that level.

The apparatus used for electrocoagulation was the standard Walker retinal detachment unit. The 1.1-mm. penetrating electrode from the Liebel-Flarsheim retinal detachment kit was used. The surface electrode was made of aluminum and designed to give a contact surface of one square mm. in area (fig. 3).

The technique of electrocoagulation in both enucleated eyes and on living animals was that employed at the hospital of the University of Pennsylvania in clinical retinal detachment surgery both in regard to intensity of current and time of application. A current of approximately 90 ma. was applied for

* All intraocular pressures in these experiments were recorded with a Schiøtz tonometer.

TABLE 1

ACCURACY OF VOLUMETRIC APPARATUS DETERMINED BY REPEATED MEASUREMENTS OF THE SAME DOG EYE

(Intraocular Pressure Constant, Schiøtz)

Eye 1	Eye 2	Eye 3	Eye 4	Eye 5	Eye 6	Eye 7	Eye 8
5.32 cc.	5.26 cc.	5.44 cc.	6.10 cc.	6.06 cc.	5.34 cc.	5.71 cc.	5.68 cc.
5.34	5.25	5.42	6.10	6.08	5.34	5.70	5.68
5.32	5.25	5.40	6.08	6.08			
5.31	5.24	5.40	6.08	6.07			
5.35	5.24	5.39	6.08	6.05			
							Average Error Between Successive Measurements = .01 cc.

TABLE 2

VOLUME OF DOG EYES AT VARIOUS INTRAOCULAR PRESSURES, DEMONSTRATING MINIMAL VARIATIONS
BETWEEN 10 AND 25 MM. HG (SCHIØTZ)

Eye No.	Too Soft to Register	Vol. Diff.	10 mm. Hg	Vol. Diff.	25 mm. Hg	Vol. Diff.	50 mm. Hg
1	5.57 cc.	.23 cc.	5.80 cc.	.01 cc.	5.79 cc.	.13 cc.	5.92 cc.
2	5.19	.57	5.76	.04	5.80	.07	5.87
3	5.04	.59	5.63	.06	5.69	.09	5.78
4	5.44	.24	5.68	.03	5.71	.06	5.77
5	5.54	.14	5.68	.02	5.70	.14	5.84
	Average Difference	.35		.03		.10	

about two seconds. The factor most variable and difficult to control in applying coagulation was the degree of wetness of the sclera.

Klein[16] has pointed out the importance of keeping the sclera moist because the electrical resistance of dry sclera is so unpredictable that control of the process is impossible and the degree of coagulation is uncertain. Pischel,[9] in discussion following his paper, implies that shrinkage of the sclera is much greater in degree when coagulation is applied to a wet field, but he believes that much of this shrinkage is temporary. Thorpe,[9] in the same discussion, warns that puncture coagulation must be carried out in a dry field or an "hour glass" eyeball will be produced by excessive shrinkage.

In our experience, a dry field would be difficult to maintain because of capillary oozing, even if it were desirable. To obtain uniform results an arbitrary number of applications of the electrodes was used for the purpose of our measurements. Fourteen surface applications were employed because dog eyes seemed to tolerate this number well. Thirty punctures were used in the experiments with penetrating electrocoagulation, a number which we felt did not exceed that used in some retinal detachment operations.

IV. EXPERIMENTAL DATA

A. SELECTION OF SPECIES

The earlier experiments were attempted upon rabbit eyes, but these were found to be entirely unsatisfactory because of the thinness of the sclera. The eyes tolerated electrocoagulation poorly, and the sclera necrosed. Measurements were also difficult because of the constant escape of intraocular fluid through openings in the thin sclera with lowering of intraocular pressure. Dog eyes were then used and found to be quite satisfactory.

TABLE 3

COMPARISON OF VOLUME OF THE RIGHT AND LEFT NORMAL DOG EYES

Intraocular Pressure Right Eye	Intraocular Pressure Left Eye	Volume Right Eye	Volume Left Eye	Difference in Volume between Eyes
10 mm. Hg	10 mm. Hg	5.94 cc.	5.98 cc.	.04 cc.
16	15	5.44	5.43	.01
13	11	5.14	4.89	.25
22	19	4.69	4.65	.04
25	25	5.26	5.26	.00
19	19	4.17	4.19	.02
17	15	4.97	4.97	.00
17	17	5.73	5.72	.01
17	17	5.54	5.53	.01
25	22	5.79	5.80	.01
25	25	5.69	5.71	.02

Average Difference .037 cc.

TABLE 4

CONTRACTURE OF ISOLATED STRIPS OF SCLERA FROM
FRESHLY ENUCLEATED HUMAN EYE FOLLOWING
ELECTROCOAGULATION OF ENTIRE EXTERNAL
SURFACE

Measurements of Strips Before Electro-coagulation	Measurements of Strips After Electro-coagulation	Percent Shrinkage in Length
19 = 5 mm.	13×3 mm.	32
43×6	24×3.5	44
21×6	13×3	38
19×6	12×4	37
44×6	24×3	45
25×6	15×3.5	40
25×6	14×3	44
28×5	18×3	36
27×6	19×3	30

Average 38.4%

The thickness of the sclera lies between that of the rabbit and the human eye.

Experiments upon the living animal required that one eye of each pair be used as a control. Equality of volume of the two eyes had to be determined. The volume of 11 pairs of eyes was measured and compared. The difference in volume between the eyes of 10 of these pairs ranged only from zero to 0.04 of a cc. (Table 3). The 11th pair differed in

Fig. 4 (Scheie and Jerome). Flattening and puckering of sclera produced by surface coagulation. (Freshly enucleated dog eyes.) (A) Rear view. (B) Side view.

size by 0.25 cc. The average difference between the two eyes of 11 pairs therefore was only 0.037 cc.

B. EFFECT OF SURFACE COAGULATION ON EXCISED STRIPS OF SCLERA

Before proceeding to experiments upon an intact eye, coagulation was performed on isolated strips of sclera from freshly enucleated human eyes. These strips contracted approximately 38 percent in length (Table 4).

C. EFFECT OF ELECTROCOAGULATION UPON INTRAOCULAR PRESSURE OF ENUCLEATED DOG EYES

Before utilizing the living animal, coagulation was carried out upon enucleated dog
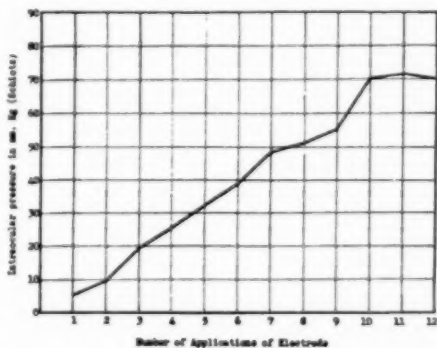
Fig. 5 (Scheie and Jerome). Effect of increasing amounts of surface coagulation upon the intraocular pressure. (Freshly enucleated dog eyes.)

eyes. Penetrating electrocoagulation was unsatisfactory in these experiments because vitreous flowed from the punctures and the eye became so soft as to render volume measurements impossible. Experiments were therefore carried out using surface electrocoagulation.

Marked shrinkage of the sclera with puckering and flattening at the site of application of the surface electrode was seen (fig. 4). The intraocular pressure rose rapidly (fig. 5). After only 4 to 6 applications of the surface electrode, the average intraocular

pressure rose from a level too low to record on a tonometer to 40 mm. Hg. After 9 or 10 applications, the intraocular pressure approached 70 mm. Hg beyond which further increase was impossible because ruptures occurred in the sclera.

These experiments confirmed previous observations regarding contracture of sclera and increase in intraocular pressure following surface coagulation. These observations also demonstrated the necessity of reducing the volume of the ocular contents during electrocoagulation to permit the sclera to contract without the resistance of increasing intraocular pressure. Therefore, in succeeding experiments, in order to maintain the intraocular pressure as nearly as possible between 15 and 25 mm. Hg, aqueous was aspirated by paracentesis with a No. 27 needle inserted through the limbus obliquely.

D. EFFECT OF SURFACE COAGULATION IN REDUCING THE VOLUME OF ENUCLEATED DOG EYES

Reduction in volume following surface electrocoagulation was studied in 11 dog eyes. The usual 14 applications of the surface electrode were used (Table 5). All of the measurements were taken with the tension within the limits noted above. If the eye

TABLE 5

EFFECT OF SURFACE COAGULATION IN REDUCING THE VOLUME OF ENUCLEATED DOG EYES
(14 Applications of Electrode)

Volume Before Coagulation	Volume After Coagulation	Reduction in Volume
4.70 cc.	3.89 cc.	.81 cc.
5.28	4.42	.86
5.32	4.52	.80
5.94	4.72	1.22
5.98	4.77	1.21
5.44	4.42	1.02
5.43	4.40	1.03
5.14	3.91	1.23
5.89	3.86	1.03
4.69	4.09	.60
4.65	3.85	.80

| | | Average Reduction in Volume .96 = 18.5% |

was too soft following coagulation, as a result of excessive paracentesis, saline solution was injected through the same fine needle to elevate the intraocular pressure to a dependable level. The smallest reduction in volume was 0.6 cc., the largest 1.23 cc. An average reduc-

TABLE 6

EFFECT OF SCLERAL RESECTION (4 ×22 MM. ELLIPSE) IN REDUCING THE VOLUME OF ENUCLEATED DOG EYES

Volume of Eye Before Resection	Volume of Eye After Resection	Reduction in Volume
4.96 cc.	4.46 cc.	.50 cc.
4.88	3.90	.98
5.11	4.39	.72
4.70	3.66	1.04
5.17	4.44	.73
6.23	5.58	.65
4.86	4.21	.65
6.04	5.55	.49
5.26	4.68	.58
4.97	4.35	.62

| | | Average Reduction in Volume .7 cc. = 13.3% |

tion in volume of 0.96 cc. or 18.5 percent of the volume of the eye resulted.

E. EFFECT OF SCLERAL RESECTION IN REDUCING THE VOLUME OF ENUCLEATED DOG EYES

Scleral resections, consisting of the removal of an ellipse of 4 by 22 mm., were performed on 10 enucleated dog eyes. The technique was the standard one for scleral resection described in some detail by Lindner.[*] The average reduction in volume was 0.7 cc. or 13.3 percent (Table 6) which was less than that occurring with the surface coagulation of enucleated eyes.

F. IMMEDIATE EFFECT OF SURFACE COAGULATION IN REDUCING THE VOLUME OF THE DOG EYE IN THE LIVING ANIMAL

One eye of each of 5 animals was prepared by incision of the conjunctiva and tenotomy of the external rectus muscle to expose the sclera. Cautery was then carried out in a

manner similar to that in the experiments on the previously enucleated eyes. Care was taken to avoid electrocoagulation of the ciliary body. Fourteen applications of the surface
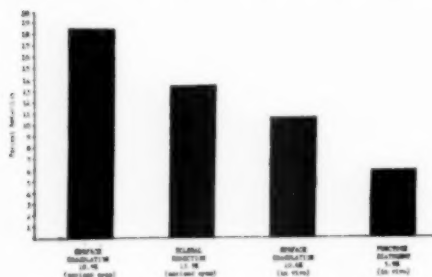
Fig. 6 (Scheie and Jerome). Comparison of reduction in volume in dog eyes produced by various operative procedures.

electrode were made. Paracentesis had to be performed to prevent the rise of intraocular pressure to an extremely high level and to permit reduction in volume. Immediately following the coagulation procedures both eyes were enucleated. The unoperated eye was used as a control for the determination of volume changes.

The average reduction in volume was found to be 0.64 cc. (12.7 percent) which was closely comparable to that obtained by scleral resection. As shown in the table, a rather marked discrepancy in results exists between the operation performed upon eyes previously enucleated and the operations done in the living animal (fig. 6). This can best be explained as due to variations in effectiveness of the electrode.

The eyes already enucleated were coagulated after moistening the area of contact with saline solution which is an excellent conductor. The amount of current delivered and the effect of each application was therefore quite uniform. In the living animal such application is more difficult because of constant oozing of blood into the field of operation and inevitable variation in the delivery of current.

G. PERSISTENCE OF REDUCTION IN VOLUME PRODUCED BY SURFACE COAGULATION

Having determined the fact that electrocoagulation of the sclera produced a reduction in volume of the eye in the living animal comparable with that of a scleral resection of a size used clinically, it seemed important to establish the duration of such changes.

To determine this, animals were operated
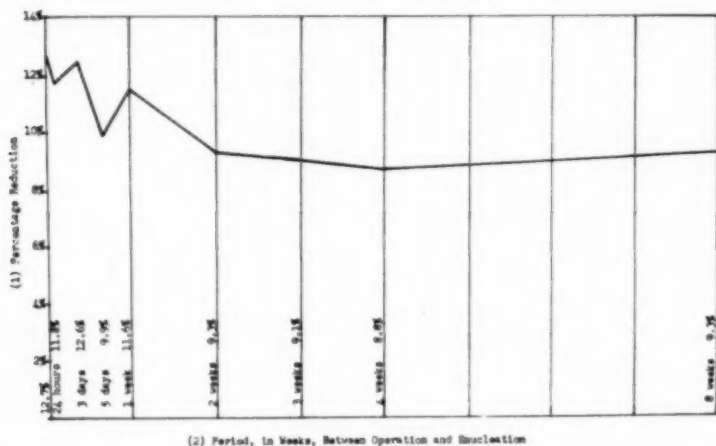
Fig. 7 (Scheie and Jerome). Relationship between (1) volume reduction of dog eyes resulting from surface coagulation and (2) period between coagulation and enucleation.

in the manner just described and the eyes of 5 dogs, were removed and measured at each of the following periods: 24 hours, 3 days, 5 days, 1 week, 2 weeks, 3 weeks, 4 weeks, and 8 weeks (fig. 7).

The reduction in volume fell slowly during the first two weeks when a reduction of approximately 0.5 cc. or 9 percent was reached. Subsequent to the second week the reduction remained unchanged and the operated eye remained smaller than the unoperated eye throughout the period of observation of two months. This was true even though both eyes appeared normal to external examination. The intraocular pressure was normal in each, except in animals subjected to short-term experiments.

H. THE EFFECT OF PENETRATING ELECTRO-COAGULATION IN REDUCING THE VOLUME OF THE DOG EYE IN THE LIVING ANIMAL

Control measurements on enucleated eyes using penetrating diathermy were unsuccessful because of the low intraocular pressure resulting from vitreous loss through the punctures. It was not possible by injecting fluid into the eye to raise the tension to a dependable level (15 to 25 mm. Hg). The fluid escaped as fast as it was injected. The same was true in experiments in the living animal where the eyes were enucleated shortly after operation. The difficulties, however, were obviated by postponing enucleation of the eyes until one week after operation. By this time the punctures had sealed and the eye could be injected so that the intraocular pressure was within the limits satisfactory for volume measurements.

Thirty applications of the penetrating electrode distributed over almost half of the scleral surface behind the ciliary body were made. The average reduction in volume by this technique was 0.26 cc. or 4.9 percent. Eyes of another group of 5 animals were enucleated 4 weeks following operation. A reduction in volume of 0.36 cc. or 6.9 percent was found.

The discrepancy between volume changes of the eyes of these two groups of animals cannot be explained. The essential fact remains that although reduction in volume with this number of applications did occur, the amount was only approximately half that produced by the technique of surface coagulation used in our experiments (fig. 6). This was undoubtedly due to the fact that a smaller area of the sclera was affected by the penetrating technique than by the surface application.

V. PATHOLOGY

Previous experimental studies on eyes treated by various perforating techniques—actual cautery (Herzfeld,[17] 1930, Luntz,[18] 1939) perforating diathermy (v. Szily and Machemer,[19] 1933, Cordero,[20] 1934), electrolysis, trephining with application of caustic to the choroid (v. Szily and Machemer[19]), and perforation with a sharp instrument (Weekers[21, 22]) have shown a general agreement as to nature and sequence of pathologic changes in the eyes so treated. Weekers especially emphasizes that the histopathologic picture is essentially the same regardless of the nature of the perforating agent. He conclusively shows that the origin of the fibrous tissue band that holds the retina so firmly in place after perforating wounds is in the episclera, and that this fibrous tissue invades the wound toward the retina in a remarkably short time after the injury.

The first stage in the sequence of the pathologic change referred to is characterized by mechanical adherence of retina to choroid at the operative site (Herzfeld[17]), edema and vascular engorgement of the sclera, choroid, and retina, outpouring of fibrin or blood into the wound, and mild inflammatory changes of the acute type, with polymorphonuclear leukocytes predominating.

These changes are followed in from 1 to 2 weeks by a second phase consisting of subacute inflammation, in which mononuclear cells predominate. The sclera loses its nuclei and begins to look necrotic, but it does not

disintegrate. Active connective-tissue pro-
liferation starting from the episclera is seen.
The choroid and retina lose their vascular en-
gorgement and pigment rearrangement oc-
curs.

The third stage is characterized by com-
pletion of a firm fibrous tissue bridge which
extends between episclera and choroid, fre-
quently reaching to or invading the retina.
Localized atrophy and thinning of sclera,
choroid, and retina are seen. The retina at
this stage is very firmly attached to the scar
beneath it.

Following surface coagulation, basic his-
topathologic changes show essentially the
same nature and sequence, according to most
observers, with the exception that the inva-
sion of the necrotized sclera by scar tissue
from the episclera is much slower and is not
mentioned by several authors as occurring
at all.

Weekers[21, 23] emphasizes that broad, fairly
firm adhesions form between retina and
choroid after surface coagulation, but he
does not mention or illustrate fibrocytic inva-
sion of the sclera as occurring with this tech-
nique, despite the fact that some of the eyes
in his series remained in vivo for 5 weeks
after operation.

Pischel[24] obtained less firm but broader
retinochoroidal adhesions using surface co-
agulation than he did with the penetrating
technique. He emphasized that changes in
sclera, choroid, and retina spread farther
from the operative site with surface coagu-
lation. The longest period between operation
and enucleation in his series is two weeks;
sections of eyes coagulated with the pene-
trating electrode show marked fibrosis into
the scleral wound, but no such change is seen
in surface-coagulated eyes.

Cordero's[20] studies of eyes enucleated in
periods ranging from 3 to 70 days after sur-
face and penetrating diathermy did not dis-
close instances of fibrous tissue invasion of
the sclera after the former method, but con-
firmed the similarity of other pathologic
changes occurring with each method. He

found that the reaction of the uveal tract and
retina is more severe to surface coagulation.
He based this conclusion on ophthalmoscopic
and microscopic evidence.

Bucallosi[25] was able to demonstrate in rab-
bit eyes that a bridge of fibrous connective
tissue connecting episclera to retina is pres-
ent one month after surface coagulation with
caustics or diathermy. He was possibly the
only investigator to describe this reaction.

Occasional or frequent concomitant
changes with both perforating and surface
technique listed by these investigators are:
vitreous opacities, corneal edema, cellular
deposits within the eye, retinal hemorrhages,
retinal folds, detachments, retinal tears, and
degeneration of retina and choroid extending
well beyond the operative sites. The fre-
quency and intensity of these reactions
seems to be directly related to the amount
of operative trauma.

A. PATHOLOGIC CHANGES OCCURRING IN
   EYES COAGULATED WITH SURFACE ELEC-
   TRODES (TABLE 7)

Slides for microscopic study were pre-
pared from most of the eyes operated during
the conduct of the volume studies. The speci-
mens were fixed in formalin, after which
they were embedded in nitrocellulose. Sec-
tions were 14 to 20 microns in thickness.
They were stained with hematoxylin and
eosin and mounted in Canada balsam. We
were thus able to follow the histologic
changes resulting from electrocoagulation at
the same periods of time used for studying
the volume changes. The sequence followed,
therefore, involved eyes of periods ranging
from those enucleated immediately after co-
agulation to those followed for as long as
8 weeks.

In general, the changes seen confirmed
those of previous observers. The histologic
changes seen in the episclera were somewhat
modified because the episcleral connective-
tissue mantle had to be dissected away as
completely as possible to permit accuracy of
volume measurements. Following removal of

Tenon's capsule and this connective-tissue mantle, the sclera appeared somewhat darkened and thinned at each site where the electrode had been applied. This was true for eyes treated with perforating as well as surface diathermy.

1. Changes in eyes removed immediately after coagulation (fig. 8). Ophthalmoscopic examination revealed white exudative areas

coagulation revealed the same white areas of retinal exudate at the site of each coagulation point. The fifth eye had a hyphemia preventing a view of the fundus. Two of the eyes had retinal detachment. A large retinal hemorrhage could be seen in one eye in the area of coagulation.

The microscopic changes were much more marked than those which had occurred in the

TABLE 7

SUMMARY OF PATHOLOGIC CHANGES RESULTING FROM SURFACE COAGULATION

Length of time Observed	Ophthalmoscopic	Histopathologic Findings			
		Coagulated Area			Associated Findings
		Sclera	*Choroid*	*Retina*	
Acute to 5 days	White retinal exudates; spotty or confluent, site of coagulation.	Edema moderate. Coagulation necrosis.	Vascular engorgement. Edema increasing.	Edema. Degeneration with irregularity of layers.	Deposits of granulocytes and pigment on corneal endothelium.
	Retinal hemorrhages in coagulated area.	Pmns, fibrin, fibroblasts on surface.	Pmns maximum at 3 days.	Vascular engorgement.	Vitreous: clumps of rbc occasional.
	Retinal detachment frequent.	New vessels occasionally.	Occasional hemorrhages.	Detachments frequent. Hemorrhages occasional.	Papilledema occasional.
1 week to 2 weeks	Retinal exudates absorbing. Retinal hemorrhages. Occasional localized retinal detachment. Vitreous opacities occasional.	Coagulation necrosis. Fibrocytes cover surface. Wbc decreasing. New vessels occasionally.	Vascularity decreasing. Edema subsiding. Pigment dispersed. Hemorrhage occasional.	Atrophy increasing. Detachment frequent. Hemorrhage occasional.	Deposits of wbc plasm cells and pigment. Same type cells in cilioscleral sinus frequently. Vitreous hemorrhage occasional.
3 weeks to 4 weeks	Retinal exudates nearly absorbed. Hemorrhages persist. Occasional retinal detachment. Beginning retinal atrophy coagulated area.	Coagulation necrosis. Fibrocytes invading necrotic region. A few new vessels.	Vascularity decreasing further. Pigment dispersal increasing. Thickening frequent. Thinning occasional.	Atrophy severe. Detachment occasional. Hemorrhage occasional.	Retina: Irregularity of layers near coagulated area occasional Ciliary Body: Plasma cells occasional.
8 weeks	Atrophy coagulated area. Pigment disturbance frequent. Hemorrhage occasionally. Vitreous opacities occasionally.	Coagulation necrosis same as at 4 weeks. Fibrocytes cover surface and invade necrotic region. Pigmentation occasionally seen.	Vascularity same as at 4 weeks. Thinning inconstant.	Atrophy severe. Detachment occasional. Firm adherence between retina and choroid frequent.	Retina: atrophy frequently extends beyond operative site.

at the site of each application of the surface electrode. The media appeared clear.

Only one eye was studied microscopically. The sclera was thickened by edema, severe engorgement of the choroidal vessels was present. Hemorrhagic foci were seen in the choroid. Retinal edema and degeneration with irregularity of the various retinal layers was present. No other pathologic changes were seen.

2. Changes in eyes removed 24 hours after coagulation. Ophthalmoscopic examination of 4 of the 5 eyes removed 24 hours after

eyes removed immediately. Coagulation necrosis had occurred; edema of the sclera was present; fibrin could be seen on the surface of the sclera; some infiltration with polymorphonuclear cells had occurred. The choroid showed marked vascular engorgement. Many polymorphonuclears were also seen, as well as a few monocytes. Edema of the choroid was present. The retina was edematous. Detachment of the retina had occurred over the coagulated site in 2 of the eyes. Pigment disturbance was present in 1 eye. The retinal vessels were engorged. A few cellular

Fig. 8 (Scheie and Jerome). Photomicrograph of section (×160) from an eye removed directly after operation showing edema and density of staining reaction at the scleral operative site, as well as edema, folding, and architectural distortion of the retina.

deposits could be seen on the corneal endothelium of 2 eyes; the iris vessels were engorged; the ciliary body was edematous in 2 of the eyes studied.

3. *Changes in eyes removed 72 hours after coagulation.* Ophthalmoscopic examination revealed little change from that in the eyes enucleated immediately and at 24 hours. Retinal hemorrhages were more common.

Microscopically, the sclera revealed little change from that in eyes removed at 24 hours. The mantle of connective tissue and cellular infiltrate over the coagulated area was probably more marked. The sclera at the operative sites now appeared slightly necrotic. The choroid was engorged and edematous. The same type of cellular infiltrate was present as at 24 hours. The retina was edematous in all eyes over the coagulated area and the various cellular layers were

irregular, as is shown in Figure 9.

One of the 4 eyes examined revealed some cellular deposits on the corneal endothelium. The iris vessels were engorged in 2 of the eyes. The ciliary body was edematous in 3 of the eyes. The choroid was diffusely edematous in 1 eye. Clumps of cells were found in the vitreous of 2 eyes.

4. *Changes in eyes removed 5 days after coagulation.* White retinal exudate and retinal hemorrhages over the coagulated areas were characteristic by ophthalmoscopic examination.

Three eyes were examined microscopically. The sclera over the coagulated area was edematous and showed necrosis. The fibroblastic mantle could be seen over the coagulated area. This contained many white blood cells and fibroblasts. The choroid in the coagulated area was edematous and hemor-

rhagic. Rather marked vascular engorgement was present.

The retina over the coagulated area was folded and edematous. Its layers again were irregular. Cellular deposits could be seen in the anterior chamber. The ciliary body was edematous and the iris showed some engorgement. The nervehead of one eye was edematous.

5. *Changes in eyes removed one week after coagulation.* Ophthalmoscopic examination revealed less retinal exudation than was present in eyes previously described. The retinal hemorrhages remained.

The sclera showed evidence of coagulation necrosis. The fibroblastic mantle was thick and completely covered the operative site. Vascularity of the choroid was decreasing. The retina showed beginning atrophy in all cases. Retinal detachment was present in two of the four eyes examined. The changes elsewhere in the eyes were little different from those recorded in the preceding groups except that one cornea showed what appeared to be an interstitial keratitis near the limbus.

6. *Changes in eyes removed 2 weeks after coagulation.* Ophthalmoscopic examination revealed absorbing retinal exudates and hemorrhages. Both phenomena were less marked than at one week.

Three eyes of those removed at the end of 2 weeks were examined microscopically. The sclera again showed coagulation necrosis and a connective-tissue mantle more heavily developed. Fibrocytes were beginning to invade the sclera in one eye. The choroid showed dispersion of pigment with dimin-

Fig. 9 (Scheie and Jerome). Photomicrograph of section (×160) from an eye removed 72 hours after operation showing coagulation necrosis of the sclera at the operative site; edema, vessel engorgement, and moderate inflammatory reaction in the choroid; fluid retinal detachment and edema and architectural distortion of the retina.

ishing vascular engorgement.

The retina was atrophic over the coagulated area with detachment present in all 3 eyes. One eye was normal outside the coagulated area; 1 showed degenerative change

eyes connective tissue was seen invading the coagulated sclera. The choroid showed less vascular engorgement with some pigment disturbance at the site of the coagulation. The retina was detached in 2 of the eyes at

Fig. 10 (Scheie and Jerome). Photomicrograph of section (×80) from an eye removed three weeks after operation showing necrotic scleral operative site; hemorrhagic retinal detachment; and "band type" retinal atrophy immediately under the operative site.

of the ciliary body near the operative site. Apparently a portion of the ciliary body had been coagulated.

7. *Changes in eyes removed 3 weeks after coagulation* (fig. 10). Ophthalmoscopic examination revealed that the white retinal exudates had nearly absorbed. Retinal hemorrhages were still present. Localized pigment disturbance was common. Localized retinal atrophy over the coagulated area could be seen in 2 of the 6 eyes.

The sclera in all of the eyes still demonstrated coagulation necrosis and formation of a connective-tissue mantle. In 2 of the

the site of coagulation. Hemorrhagic exudate was present beneath the detachment in each of these eyes.

Retinal atrophy was marked over the coagulated area in 5 of the eyes. The ciliary body showed pigment disturbance and some atrophy in 2 eyes in which the coagulation was near this region. The other eyes were normal elsewhere than at the site of coagulation.

8. *Changes in eyes removed 4 weeks after coagulation.* Ophthalmoscopically the hemorrhages were less marked and retinal atrophy was much more obvious.

The sclera in all 3 of the eyes examined microscopically showed coagulation necrosis and again the connective-tissue mantle. Fibrous tissue now extended deeply into the necrotic sclera in all 3 eyes. The choroid and retina both showed irregular atrophy over the coagulated area. The eyes were essentially normal otherwise, although the ciliary body adjacent to the site of the coagulation

B. PATHOLOGIC CHANGES OCCURRING IN EYES COAGULATED WITH PENETRATING ELECTRODES (TABLE 8)

A study of these eyes was made in an attempt to prove or disprove the observation of Weekers that fibroblastic tissue from the episclera migrated inward toward the choroid and retina through the puncture holes. From our observations described
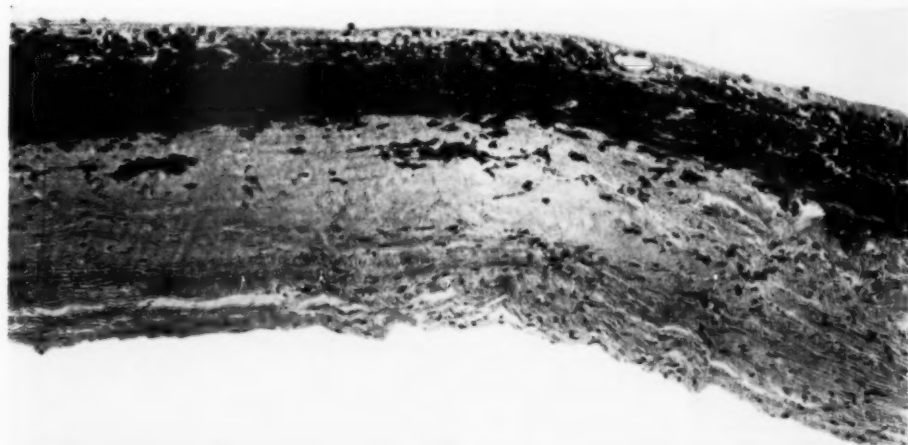
Fig. 11 (Scheie and Jerome). Photomicrograph of section (×160) from an eye removed eight weeks after operation showing advanced cicatrization about the scleral operative site and confluence of the margins of the sclera, sclerotic choroid, and atrophic retina. Note dense episcleral "mantle" of fibrous tissue over necrotic zone of sclera.

showed some pigment disturbance and probably atrophy.

9. *Changes in eyes removed 8 weeks after coagulation* (fig. 11). Retinal hemorrhages were seen in but 1 eye ophthalmoscopically. These were small and deep. Retinal atrophy was present.

Microscopically, necrosis of the sclera was still visible. The area of necrosis was covered and deeply invaded by fibrous tissue. The choroid showed diminished vascularity and atrophy over the coagulated sites. The retina was similar. Retinal detachment with subretinal hemorrhagic exudate was seen in 2 of the eyes. A vitreous hemorrhage was found microscopically in 1 of the eyes.

above, we could well predict that Weekers's observations would be confirmed because one of the earliest phenomena following electrocoagulation of the sclera is the formation of the fibroblastic connective-tissue mantle.

This fibroblastic mantle in the early stages involved only the surface of the sclera. In 1 of 6 eyes at the end of 3 weeks and in all eyes at 4 weeks, it was shown that these fibroblastic cells invaded the necrotic sclera itself. Presumably this invasion would have occurred much more promptly and earlier had openings been provided into which fibroblasts might grow.

In the microscopic study of the eyes coagulated with penetrating diathermy, the

same intervals were used as for volumetric measurements; namely, 1 and 4 weeks.

1. Changes in eyes removed one week after penetrating coagulation (fig. 12). Ophthalmoscopic examination. Vitreous opacities were seen in 1 eye of 4 examined. All eyes had soft white retinal exudates surrounding each puncture. Two eyes showed depigmentation near the puncture sites. In 1 eye a small hemorrhage was seen.

Three eyes were examined microscopi-

moscopic examination: Two of 5 eyes had nonfloating vitreous striae over and attached to the coagulated area. In all 5, chorioretinal atrophy was seen around each puncture. In one case the atrophic areas were partially confluent, while, in another, a soft white exudative appearance was superimposed on the atrophy.

All 5 eyes were examined microscopically. All showed scleral coagulation necrosis at the operative site; 3 had a substantial core

TABLE 8

SUMMARY OF PATHOLOGIC CHANGES RESULTING FROM PENETRATING COAGULATION

Length of time Observed	Ophthalmoscopic	Histopathologic Findings			
		Coagulated Area			Associated Findings
		Sclera	*Choroid*	*Retina*	
1 week	White retinal exudates sites of coagulation; occasionally confluent. Pigment disturbance at coagulated site occasionally.	Coagulation necrosis at operative sites traversed by core of fibrocytes extending from fibrous mantle on surface deep into sclera. Monocytes in necrotic area.	Moderate pigment choroid dispersal. Necrosis occasionally. Fibrosis occasionally.	Moderate necrosis or degeneration with irregularity of layers. Occasional hemorrhage. Occasional small detachments.	Essentially normal.
4 weeks	Chorioretinal atrophy at each coagulated site; occasionally confluent. Striated vitreous opacities occasionally. Occasional retinal hemorrhage or persisting exudate.	Coagulation necrosis at operative sites traversed by core of fibrocytes extending down from episcleral fibrous mantle, reaching to choroid or even retina.	Degeneration or atrophy localized to operative sites. Decreased vascularity. Pigment disturbance occasionally.	Localized atrophy. Close adherence to choroid at operative sites.	Ciliary body: Pigment disturbance, irregularity of structure occasionally.

cally. All showed scleral coagulation necrosis at the operative site traversed by a core of fibrous connective tissue which appeared to arise from an episcleral fibrous-tissue mantle and extended almost to the choroid or invaded its substance. Pigment dispersion at the operative site was uniformly present in 1 eye.

The retina under the puncture site in 1 eye was normal; in another it was necrosed and had a small hemorrhage; in a 3rd, fibrosis had extended into its substance from the episclera and through the choroid; small hemorrhagic detachments were present near the operative site in this eye. There were no abnormal findings in the other structures of these eyes.

2. Changes in eyes removed 4 weeks after penetrating coagulation (fig. 13). Ophthal-

of fibrous connective tissue reaching from a fibrous episcleral mantle down to choroid or retina. In the 4th eye the sclera at the operative site was thinned, the episcleral fibrous tissue was vascularized and there were only a few fibrocytes in the depth of the sclera. In the 5th eye the episcleral tissue was itself necrotic.

The choroid at the operative site was degenerating or atrophic in all eyes, with decreased vascularity and pigment disturbance the rule. In 1 eye, a small inward proliferation of pigmented tissue from the choroid was seen. In all 5 eyes the retina showed a bandlike atrophy confined to the operative site. In all cases it was in firm apposition with the choroid at these points.

Findings in the other structures of these eyes included pigment disturbance and mild

degeneration of the ciliary body when a coagulation was placed near its pars plana. Hyalinosis of the ciliary processes was present in another eye. One eye showed corneal bleb formation, mild degeneration of the ciliary body, and pigment deposits in the anterior chamber. One eye showed keratitis of the anterior third of the corneal stroma. Inexplicably, a small vascularized central corneal staphyloma was seen grossly in another eye.

Fig. 12 (Scheie and Jerome). Photomicrograph of section (×160) removed one week after operation showing well-marked episcleral "mantle" of fibrous tissue and an intermediate stage of healing with penetration of connective tissue core through necrotic sclera to underlying chorioretinal mass which itself shows atrophy and fibrous tissue formation. Note edema and early necrois of surrounding retinal tissue.

Fig. 13 (Scheie and Jerome), Photomicrograph of section (×160) removed one month after operation showing marked episcleral fibrosis and healed penetrating diathermy wound. There is underlying choroidal and retinal fibrosis and retinal atrophy. Note close adhesion of chorioretinal tissue to scleral scar at the operative site.

VI. Discussion

The work reported herein was undertaken to determine the amount of scleral shrinking which could be produced by electrocoagulation of the sclera and to compare these results with those obtained by experimental scleral resection. A method for measuring the volume of an eye through a fluid-displacement technique was devised and found to be reasonably accurate. The work was done upon the dog eye because the sclera was thicker and more like that of man than was that of the rabbit.

Surface and puncture diathermy were used in different experiments. Surface diathermy produced marked shrinkage and puckering of the sclera at the site of application with rapid rise of intraocular pressure signifying reduction in volume. In enucleated eyes, the tension could be elevated to 70 mm. Hg. beyond which scleral ruptures would occur and the tension would rise no higher. These experiments confirmed the observations of several workers who had

noticed a similar rise in intraocular pressure during cyclodiathermy.

To ascertain the amount of volume change which could be produced, paracentesis of the anterior chamber had to be done permitting the sclera to shrink. Fourteen applications of a surface electrode which had a contact surface of one square mm. were used in all surface coagulation experiments. An average reduction of 0.96 cc. or 18.5 percent of the volume resulted in experiments on 10 enucleated dog eyes. This was approximately 0.25 cc. more than that produced by scleral resections of 4 by 22 mm. also performed on enucleated dog eyes. The same amount of coagulation on the living animal was somewhat less effective, the average reduction in volume being 0.64 cc. Subsequent experiments demonstrated that this volume change fell during the first 2 weeks to about 0.5 cc. or 9 percent, after which, during our observation period of 2 months, the volume remained unchanged.

The effect of electrocoagulation with the penetrating electrode was then studied. Thirty applications were used, which was felt to be within the range of at least some operations for the clinical treatment of retinal detachment. These eyes were studied and a reduction of about 6 percent in volume was found, about two thirds that of the reduction obtained by surface coagulation. Because a smaller total area of sclera was coagulated, the reduction in volume by penetrating diathermy was less than that produced by surface diathermy. Even so the amount was not insignificant.

An objection to these observations can immediately be raised, for it is certainly not a common observation that the refraction of an eye operated upon for retinal detachment undergoes a marked change in refraction toward the hyperopic side, as one might expect. This we are unable to rationalize, unless the change in volume results from a flattening of one side of the eye, rather than a shortening of the anteroposterior diameter. It does seem certain, however, that at

least some degree of scleral shrinking is produced with every electrocoagulation operation for retinal detachment and suggests that further study ought to be done to devise more effective means of shortening by electrocoagulation. The present experiments tend to explain the advantages claimed for surface coagulation and possibly also serve as an argument for Langdon's[28] thermophore technique.

The pathologic studies carried out, in general, confirm those of previous observers. The sclera, choroid, and retina became edematous and engorged shortly after coagulation. The sclera had a coagulated appearance. Changes of acute inflammation presented, which in from 1 to 2 weeks transformed to a subacute appearance with mononuclear cells. Finally, fibroblasts proliferated throughout the area, and the sclera, choroid, and retina underwent atrophy in varying degrees.

Weekers's[22] work demonstrating a fibroblastic plug growing toward the choroid and retina through the opening in the sclera made by the penetrating electrode was confirmed. This seems of great importance since it causes the retina to adhere firmly to the choroid following such operations. Similar changes tend to occur following surface diathermy but the fibroblasts grow through necrotic sclera and hence the process takes place much more slowly, requiring 1 or 2 months. After using the penetrating technique, the plug can be seen as early as 1 week postoperatively.

The changes which occurred following surface diathermy, where the coagulation was more extensive and intense, were more severe than those following the penetrating technique. The engorgement of the retinal vessels, particularly in the nerve-fiber layer, was more marked. The appearance of these engorged vessels might well explain the common occurrence of preretinal and vitreous hemorrhage, seen clinically, following too heavy coagulation of the sclera.

The changes ensuing after surface dia-

thermy, where the volume changes were marked, were such that one would be hesitant to use this degree of coagulation clinically. Not only was the engorgement of vessels pronounced, but the final retinal atrophy was considerable, and, although the eyes were negative externally, their histologic appearance would counsel caution.

In conclusion, it can be stated that electrocoagulation is capable of producing a high degree of scleral shrinkage manifest by reduction in volume of the eye. This undoubtedly occurs to some degree in every operation for retinal detachment by the electrocoagulation technique.

Experimentally, surface diathermy produces more scleral shrinkage than penetrating diathermy, no doubt because a greater area of the sclera is affected. However, the pathologic changes resulting from surface coagulation are of such a severe nature that clinical application to the same extent would probably be inadvisable.

Further work should be done to devise a technique which would produce scleral shrinkage yet be less destructive to the underlying choroid and retina because there seems sufficient evidence to believe that reduction in volume of the scleral shell is of at least supplementary value in retinal detachment surgery.

VII. SUMMARY

1. The value of scleral resection is discussed.

2. Surface electrocoagulation was found to produce a reduction in ocular volume in enucleated eyes and eyes in the living animal comparable to scleral resections of 4 by 22 mm. Penetrating electrocoagulation produced a smaller reduction in volume.

3. The reduction in ocular volume resulting from electrocoagulation persisted during the period of observation of 2 months.

4. Electrocoagulation of the amount used in these experiments produced pathologic changes of such a nature as to suggest caution in its clinical use.

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DISCUSSION

DR. JONAS S. FRIEDENWALD (Baltimore, Maryland): I think we are all familiar with the fact that, after successful detachment operations, the area of the fundus that has been cauterized is often visible with a higher plus lens than corresponding areas in other parts of the periphery, but in general the axial refraction is not significantly changed. I would like to ask Dr. Scheie, therefore, whether the contraction that he gets is not rather a flattening of the sclera at the point of cauterization than the general reduction in radius of the eyeball that one gets with the scleral resection.

DR. CONRAD BERENS (New York, New York): I should like to ask Dr. Scheie whether he tried the Walker bident using the back part of it, not the points? We have thought that we got better shrinkage of the sclera by using the back of the Walker bident than by using the individual electrodes or the two points in contact with the sclera. It certainly seems to work out in practice that way, although scientifically I cannot say why shrinkage is greater than with two points introduced separately.

DR. DAVID G. COGAN (Boston, Massachusetts): It is of interest to note that the white opacification of the retina from surface diathermy of the sclera is much more extensive during the diathermy than immediately following it. This suggests that the retinal opacification is not, as generally assumed, one of coagulation. With the diathermy applied to the sclera of an excised and bisected eye, it can be shown that the opacification is due, in some measure at least, to the formation of numerous bubbles in the retina, bubbles which, when massaged out, leave the retina transparent.

DR. SCHEIE (closing): The question which Dr. Friedenwald raised occurred to us. We certainly haven't seen a marked degree of hyperopia occurring in our patients with operations for retinal detachment, and the only way to explain it is just as Dr. Friedenwald has. Marked flattening of one side rather than of the anteroposterior diameter of the eye can be seen in the slides of animal eyes.

In reply to Dr. Berens, we have not used the Walker bident.

INTRAOCULAR HEMORRHAGES IN YOUNG RATS ON CHOLINE-DEFICIENT DIETS[*]

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Toronto, Ontario

Best and Huntsman (1932) demonstrated that choline or a precursor was essential in the diet of rats to prevent the accumulation of excess amounts of fat in the liver. Later, Griffith and Wade (1939) reported hemorrhagic degeneration of the kidneys of weanling rats deprived of dietary choline. The renal lesion was usually responsible for the animal's death within two weeks. These authors also noted intraocular hemorrhage in the animals whose kidneys were most severely affected.

Christensen (1940) stated that this intraocular hemorrhage occurred mainly from the blood vessels of the ciliary body and iris. Engel and Salmon (1941) reported that the hemorrhage "appeared to originate in the ciliary vessels and spread into the posterior chamber." They also demonstrated the presence of uremia in the rats by determinations of the levels of the nonprotein nitrogen in the blood, and by the xanthydrol reaction applied to sections of brain. All the foregoing investigators were interested primarily in the renal, rather than the ocular, lesions.

The first investigations concerned mainly with the ocular changes were those of Bellows and Chinn (1943). They found that 10 to 33 percent of their animals showed some type of ocular hemorrhage, usually within the 48 hours preceding death. The most frequent form was a column of blood in Cloquet's canal; the next, was a "hemorrhage apparently arising in the region of the ciliary body, and shortly spreading beyond the crystalline lens." Less commonly, hemorrhages visible to the naked eye appeared as hyphemia.

Microscopically, they noted that the vessels of the eyeball were generally engorged, and that the ciliary processes were swollen and frequently hemorrhagic. They found free blood most often between the anterior limiting membrane of the vitreous and the crystalline lens, and not uncommonly in the anterior chamber. Puppies on the same diet developed fatty livers, but hemorrhagic degeneration of the kidneys, eyes, and other organs did not occur.[§]

The present paper will deal with further observations regarding the intraocular hemorrhages occurring in weanling rats on diets low in choline, and after nephrectomy. The results are based on observations involving more than 350 albino rats of the Wistar strain.

METHODS

DIETS

Two diets were used. Diet A (Lucas; 1948) is extremely low in choline and its precursors, but is believed to be adequate in all other respects. Diet B (Lucas; 1948) is somewhat less deficient in lipotropic agents, but is believed to be adequate in all other respects except possibly in certain amino acids. This diet takes 1 to 2 days longer to produce its results in weanling rats than does diet A. The animals were fed these diets at pleasure in each instance.

EXAMINATIONS OF LIVING ANIMALS

A small percentage of the hemorrhages were visible to the naked eye in the form

[§] Since this paper was prepared, these findings of Bellows and Chinn have been confirmed by Brückner, R., and Viollier, G.: Helvet. physiol. acta, 6:3, 1948.

Fig. 1 (Burns and Hartroft). Section of one eye of a choline-deficient weanling rat, cut in plane No. 1 indicated in Figure 10. Masson trichrome stain (×35).

of hyphemia. A few additional ones could be seen with the aid of transillumination. However, the majority could be visualized only by means of the ophthalmoscope.

For this purpose, mydriasis was obtained by the instillation of 1 drop of 2-percent homatropine in each eye. When examinations were to be made at very frequent intervals, in an attempt to obtain greater duration of mydriasis and to reduce the number of instillations required, 1-percent atropine sulfate was substituted. This was not particularly successful as the rat possesses relatively enormous reserves of "atropinase." The mydriasis following instillation of 1 drop of 1-percent atropine rarely lasted for 2 hours.

At first, it was found necessary to anesthetize the animals in order to keep them suf-ficiently still for satisfactory examination. Later, with increasing experience, it was possible to dispense with anesthesia in the young animals, especially those which were ill. For rats of 35 to 45 gm., 0.5 cc. of an 0.44-percent solution of sodium pentothal in saline was used.

POSTMORTEM EXAMINATIONS

a. Microsections

The whole eye was subjected to preliminary fixation in Bouin solution for approximately 4 to 6 hours. A small calotte was then removed from the equatorial region of the sclera, and fixation in Bouin solution continued for another 12 to 24 hours. The

Fig. 2 (Burns and Hartroft). High-power view of the marked square in Figure 1. This shows the main stem of the hyaloid system (upper left) and one of the main retinal arteries (lower right) at a point just anterior to their common origin from the central artery of the optic nerve.

tissues were dehydrated and cleared in as-
cending strengths of dioxane and embedded
in paraffin.

In a preliminary experiment only random
sections in the coronal or sagittal planes
were prepared, but it was apparent from
these that more information would be ob-
tained from serial sections cut in the frontal
plane.

Accordingly, such were prepared in subse-
quent experiments and over 10,000 indi-
vidual sections of this type were studied.
Masson's trichrome stain was used routinely,
as this facilitates rapid detection of collec-
tions of red blood cells. Selected sections
were also stained with hematoxylin and
eosin. Additional eyes were sectioned with
the freezing microtome following formalin-
fixation, and stained with Sudan IV.

Fig. 4 (Burns and Hartroft). High-power view
of marked square in Figure 3. This includes four
branches of the hyaloid artery just distal to their
origin. Note the small size and thin wall of the
lowermost branch.

b. Whole mounts

1. Benzidine and benzyl benzoate. As a
supplement to the study of cytologic detail by
the above methods, the architectural patterns
were established using whole mounts. For
this purpose, the eyes were enucleated and as
much as possible of the extrascleral tissue
was removed. Fixation was in 5-percent
formol-saline for 24 to 48 hours, a small
equatorial calotte being removed after the
first 4 hours to aid penetration. This was
followed by 6 to 12 hours' washing in tap
water. The eyes were then treated with a
modification of Ziegler's (1945) benzidine
process for staining red blood cells. Clear-
ing of the tissue was subsequently performed
by a method already described by one of us
(Hartroft; 1941).

Fig. 3 (Burns and Hartroft). Low-power view
of one eye of a choline-deficient weanling rat, cut
in plane No. 3 indicated in Figure 10.
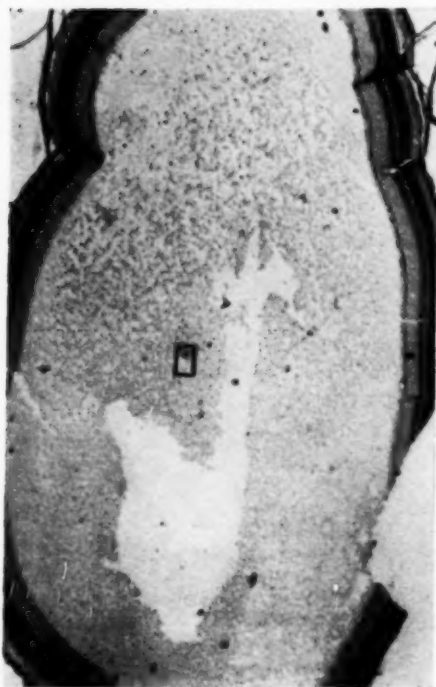
Fig. 5 (Burns and Hartroft). This illustrates an accumulation of fibrin and platelets (without red blood cells) surrounding a hyaloid vessel. (Plane No. 5 in Figure 10.)

The modifications of Ziegler's method were: (a) Shorter fixation period, (b) weaker formalin solution, (c) much longer period of washing, and (d) reduction of the strength of hydrogen peroxide in his solution "B" from 30 percent to 3 percent. This modified process produced less heavily stained specimens which were more satisfactory for photography.

2. *India ink and benzyl benzoate.* This method was used to study distribution and patency of the vascular system of the eye. The heparinized and anesthetized animal was perfused first with saline and then with a diluted, filtered, ammoniacal suspension of India ink.* The eyes were subsequently fixed, dehydrated, and cleared as above. All

* Higgins American India ink.

whole mounts were immersed in benzyl benzoate and examined under the binocular dissecting microscope.

EXPERIMENTS

In a preliminary experiment, 20 rats weighing 36 to 42 gm. were fed diet A. They were examined daily by ophthalmoscope. After they died or were killed, random sections of their eyes were prepared.

In the next experiment, 63 animals of similar weights were placed on the same diet and similarly examined except that the eyes were sectioned serially in the frontal plane. Some of those eyes which had shown no evidence of hemorrhage ophthalmoscopically were prepared as whole mounts following benzidine staining.

An additional group of 81 weanling rats were fed diet B and ophthalmoscopic exami-
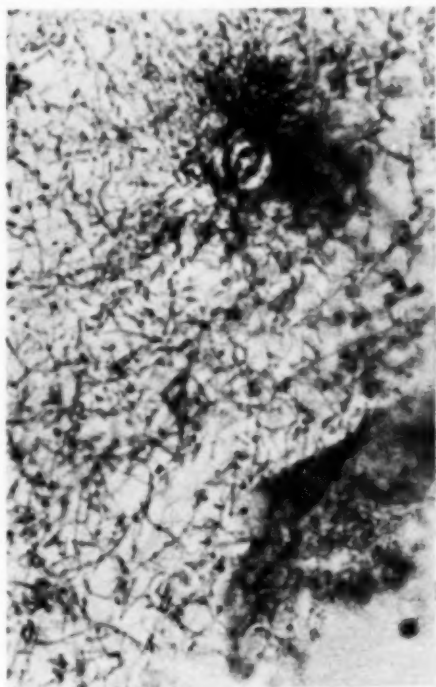
Fig. 6 (Burns and Hartroft). High-power view of marked square in Figure 5.

nations were carried out at appropriate intervals.

To study the possible relation between renal function and this particular form of intraocular hemorrhage, 20 weanling rats were rendered uremic by another means, namely bilateral nephrectomy. Ophthalmoscopic examination was carried out at frequent intervals. The eyes of two animals were serially sectioned for comparison with those of choline-deficient rats and the remaining eyes prepared as benzidine-stained whole mounts.

A group of 20 young adult rats (145-172 gm.) were fed diet A and examined ophthalmoscopically at biweekly intervals over a period of 4½ months. Twenty similar rats were bilaterally nephrectomized and ex-

Fig. 8 (Burns and Hartroft). High-power view of marked square in Figure 7. This shows the hyaloid artery near the posterior pole of the lens surrounded by fibrin and platelets with an adjacent large area of hemorrhage.

amined frequently by ophthalmoscope. Seventeen comparable normal animals and three weighing 400 to 450 gm. were perfused with India ink and the eyes prepared as unstained whole mounts.

To investigate the possible correlation between ocular hemorrhages and blood levels of N.P.N. in the choline-deficient weanling rats, 30 animals were fed diet A. These were examined ophthalmoscopically at intervals during the first 5 days and daily thereafter. Samples of tail blood were taken at the same times for estimation of nonprotein nitrogen.

Thirteen weanling rats were placed on diet A and a similar group on diet B. Ophthalmoscopic examination was performed daily during the first 4 days and more frequently

Fig. 7 (Burns and Hartroft). The darkly stained central structure is a tangential section of the crystalline lens near its posterior pole. (Plane No. 7 in Figure 10.)

thereafter. The nonprotein nitrogen level in the blood of each animal was determined as soon as ocular hemorrhage was noted.

Finally, 11 weanling animals were bilaterally nephrectomized and examined ophthalmoscopically at frequent intervals. Whenever an intraocular hemorrhage was noted, the level of the nonprotein nitrogen was determined.

ratio varying from 1:1 to 3:1 in various groups.

B. *Site and morphology.* Almost all of the hemorrhages noted in the foregoing experiments were in the vitreous humor or between it and the crystalline lens. An exception was the retinal hemorrhage shown in Figure 9, which occurred in an animal fed diet A.
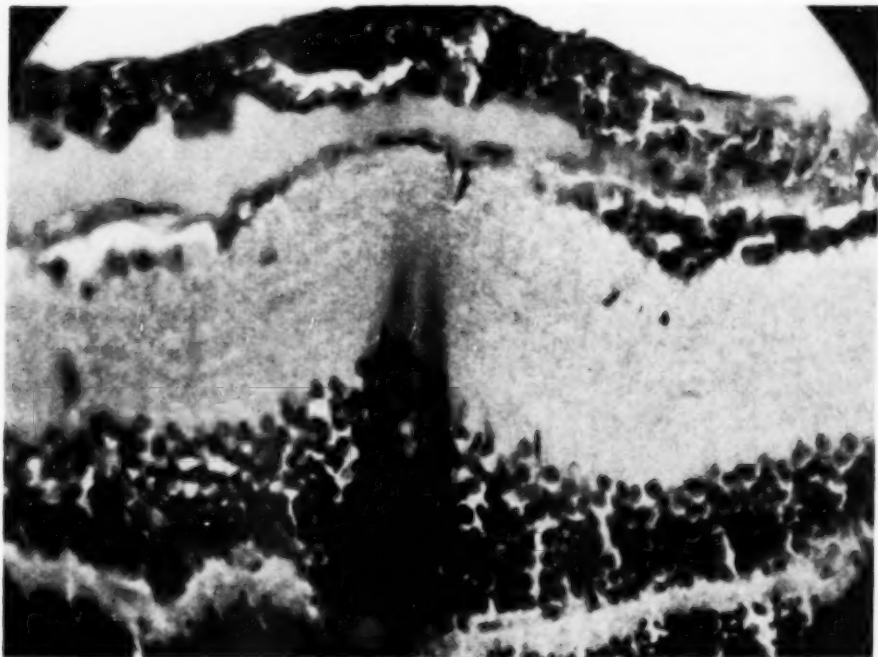
Fig. 9 (Burns and Hartroft). This demonstrates a superficial retinal hemorrhage (top) in a weanling rat fed diet A for seven days. This was the rarest situation in which these intraocular hemorrhages were observed. All others were found around branches of the hyaloid artery. See Figures 1 to 8. (Hematoxylin and eosin stain. ×375).

RESULTS

A. Incidence. In the various dietary experiments, intraocular hemorrhage occurred in one or both eyes of 35 percent to 85 percent of the animals. The difference in the two diets employed did not significantly affect the incidence; nor did the sex, although the females showed a tendency to greater susceptibility than the males, the

A hyaloid arterial system was found in each of the 75 eyes which were serially sectioned. The hyaloid vessels can usually be seen ophthalmoscopically, and in normal eyes they appear as slightly irregular, highly refractile lines. In the hemorrhagic eyes they are surrounded for considerable portions of their lengths by a granular, pale-red sheath (stereoscopic fig. 11). Larger areas of hem-

orrhage are seen as rather "fluffy" enlarge-ments of this sheath, varying greatly in size and density (stereoscopic fig. 12).

Microscopically, also, the commonest site of hemorrhage was between the vitreous and the crystalline lens. The blood and the ac-

C. Hemorrhage following nephrectomy. Sixteen of 20 weanling rats (80 percent) suffered hemorrhage in one or both eyes fol-lowing bilateral nephrectomy. Only 3 of 23 eyes with patent hyaloid arteries were free from hemorrhage. Collections of red cells
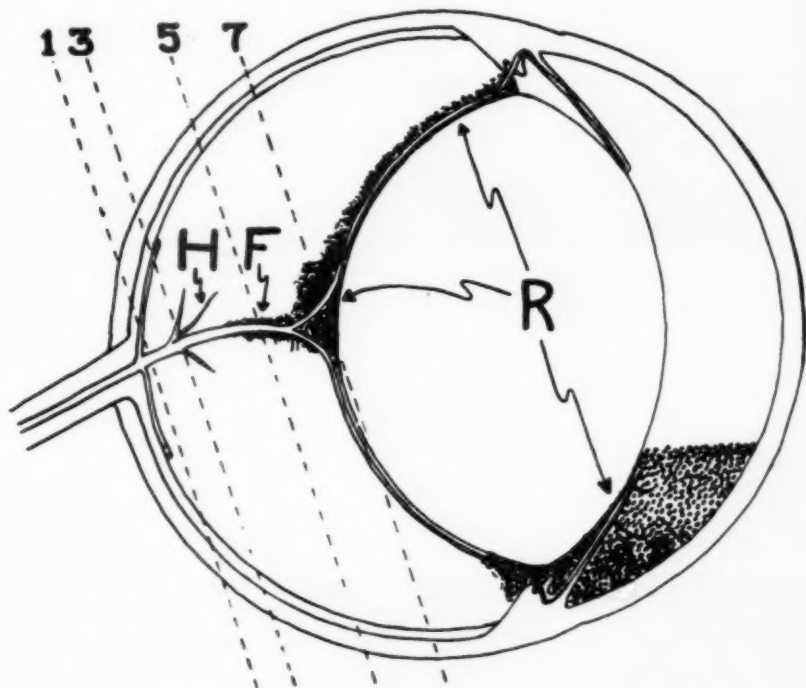
Fig. 10 (Burns and Hartroft). This is a two-dimension, graphic reconstruction of the eye illustrated in Figures 1 to 8. An additional hemorrhage has been shown originating in the ciliary region and extend-ing into the anterior chamber with resultant hyphemia. (H) Hyaloid artery. (F) Fibrin and platelets (without red blood cells). (R) Red blood cells with fibrin and platelets. The dotted lines indicate the planes of the sections illustrated in the correspondingly numbered photomicrographs (figs. 1, 3, 5, and 7).

companying fibrin lay, in almost every case, around the hyaloid artery, or one or more of its branches. In a few cases there were extensions of blood to the ciliary region, and around the lens into the aqueous chambers. Occasionally, hemorrhages limited to the ciliary region were found. In 13 eyes of 10 animals fibrin and platelets without red blood cells were seen adjacent to the hyaloid vessels (fig. 1 to 8 and fig. 10).

could not be demonstrated in any of the eyes without functional hyaloid arteries. Those hemorrhages present were ophthal-moscopically and microscopically identical with those seen in the animals on choline-deficient diets (stereoscopic fig. 13).

D. Older animals. Animals, 150 to 170 gm. in weight, fed diet A for $4\frac{1}{2}$ months, did not develop ocular hemorrhages; nor did those which were bilaterally nephrecto-
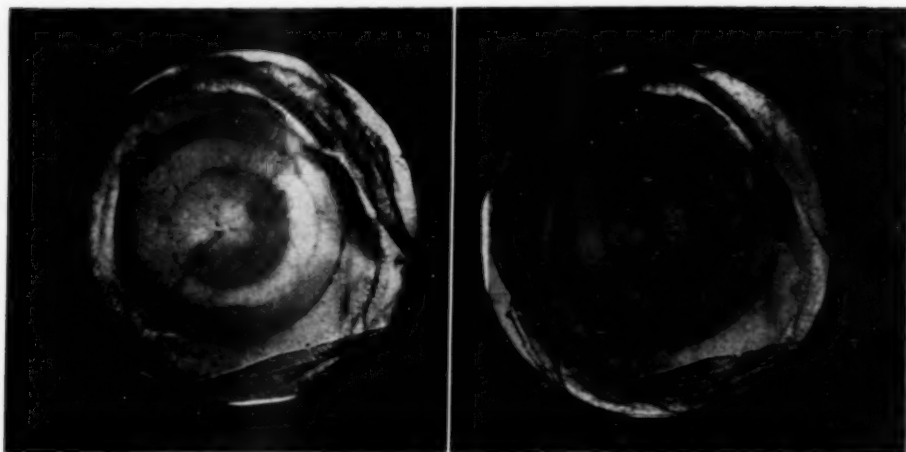
Fig. 11 (Burns and Hartroft). Stereoscopic photomicrograph (×12). This shows an eye from a choline-deficient weanling rat viewed through the pupil. Note the granular sheathing of the hyaloid vessels (lower left and upper right).

mized but fed normal diets. However, examination of the whole mounts from the latter experiment indicated that although the hyaloid artery was present in most of the eyes, it was usually nonpatent. This was confirmed by the India-ink injections, for in only 1 of the 40 eyes examined was any indication of patency found. Even this was limited to a relatively short portion of one of the smaller branches.

E. N.P.N. experiments. Of the first group of animals in which the blood levels of
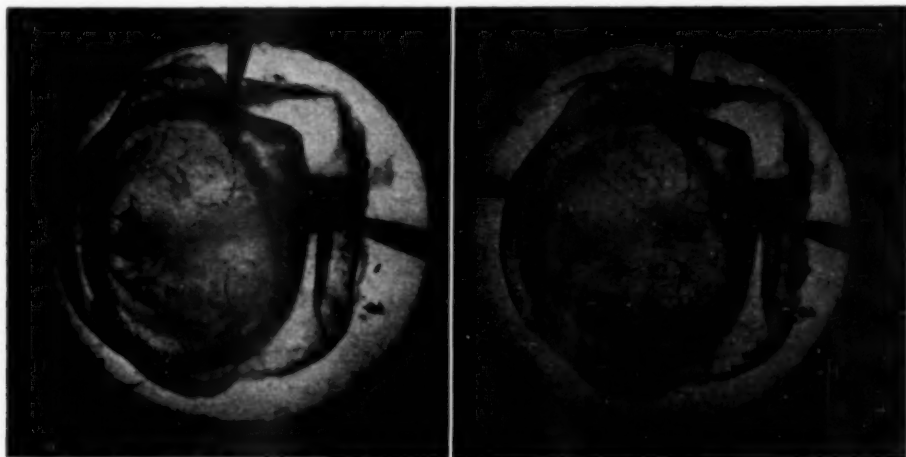
Fig. 12 (Burns and Hartroft). Stereoscopic photomicrograph (×12). This demonstrates, in a similar specimen to that of Figure 11, a small hemorrhage at the left near the periphery of the lens. A hyaloid vessel can be seen passing across the posterior surface of the lens, through the area of hemorrhage and beyond it to the ciliary body. This view is taken obliquely from behind.

N.P.N. were followed from day to day, 20 (67 percent) developed intraocular hemorrhage in one or both eyes. In 4 of these, the level of nonprotein nitrogen in the blood was within or near normal limits at the time the hemorrhage was first discovered.

In the others it was moderately to markedly increased, but there was no consistency in the levels at which hemorrhage appeared. The hemorrhages which were

nonprotein nitrogen levels in the blood of 3 of these were normal or nearly normal, while those of the remainder were moderately or markedly elevated.

In the bilaterally nephrectomized group, 5 of the 11 (45 percent) weanling rats developed intraocular hemorrhage. In every case the nonprotein nitrogen level in the blood was markedly increased at the time the hemorrhage was discovered.
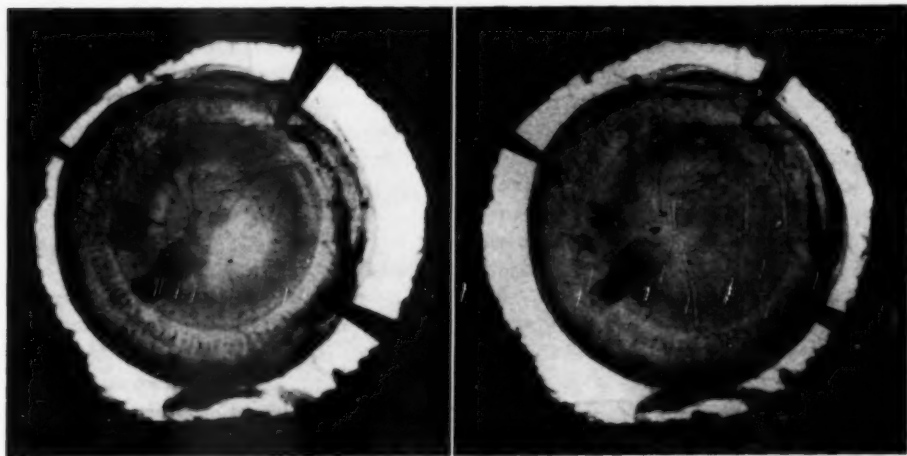
Fig. 13 (Burns and Hartroft). Stereoscopic photomicrograph (×12). This depicts two hyaloid vessels, each with a small hemorrhage in an eye from a bilaterally nephrectomized weanling rat fed a normal diet. Note the close resemblance of this lesion to those illustrated in Figures 11 and 12 showing hemorrhages in choline-deficient animals. The photographs were taken through the posterior pole.

found in the presence of normal blood levels of N.P.N. occurred on the 4th to 7th days of the experiment. Hemorrhages found in animals with increased concentrations of N.P.N. in the blood occurred on or after the 7th day. The pattern of the N.P.N.-time curve was essentially the same in all animals regardless of the time of hemorrhage. A typical example is illustrated in Graph 1.

In the second group consisting of 13 animals fed each diet (A and B), no essential differences were noted, except that elevation of the blood N.P.N. did not occur as soon in animals fed diet B as those fed diet A. Seventeen of the 26 animals (65 percent) developed intraocular hemorrhages. The

DISCUSSION

There is strong evidence in the foregoing results to show that the intraocular hemorrhage occurring in weanling rats, both on choline-deficient diets and following bilateral nephrectomy, originates from the hyaloid arterial system. Hemorrhages limited to the ciliary region are considered to have originated from the more peripheral portions of the branches of the hyaloid artery, rather than from the vessels within the ciliary body. The capillary dimensions of hyaloid vessels make their detection difficult, especially in the peripheral portions. This difficulty is increased if large amounts of fibrin and blood surround them.

Blood in all the locations mentioned by previous investigators and confirmed by us can be explained on the basis of hemorrhage originating from the hyaloid system. The only exception is the rare retinal hemorrhage. The hyaloid vessels are unusual, for although of the order of arterioles in their position in the vascular tree, their structure resembles that of capillaries. The thin walls,

suggests that choline deficiency produces intraocular hemorrhages in weanling rats through the medium of the renal lesions.

Although older rats have frequently been fed choline-deficient diets, no case of intraocular hemorrhage has been reported in such animals and we have found none. Adult rats on a choline-deficient diet do not develop such severe and fulminating renal lesions
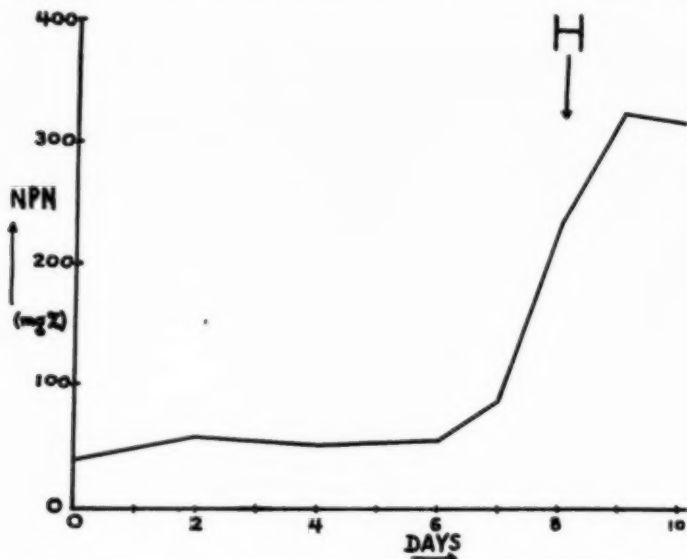
Graph 1 (Burns and Hartroft). This is a typical example of the graphs obtained by plotting the N.P.N. levels of the blood against the number of days weanling rats were fed diet A. (H) indicates the time intraocular hemorrhage was first noted.

subjected to arteriolar pressures and supported only by the vitreous, would appear to be uniquely susceptible to hemorrhage.

The distribution of the extravasated blood extending along the vessels and the presence of fibrin and platelets without red blood cells, in some situations, suggest diapedesis, rather than actual interruption of the continuity of the vessel wall in the early stages. The later formation of "fluffy" hemorrhages may be associated with actual rupture of the vessel wall.

The occurrence of morphologically identical hemorrhages in bilaterally nephrectomized animals on normal diets strongly

as do the weanlings. The lack of patency of the hyaloid arteries appeared to be the probable reason why the older animals did not develop intraocular hemorrhage following bilateral nephrectomy. The failure of such animals to develop the hemorrhages on the choline-deficient diet could thus be explained in either of two ways; (1) On the basis of insufficient interference with renal function, and (2) By the lack of patency of the hyaloid arteries.

The occurrence of ocular hemorrhages in 7 animals with normal levels of nonprotein nitrogen in the blood appears to contradict the theory that the hemorrhages are asso-

ciated with renal dysfunction. It must be remembered, however, that determinations of blood N.P.N. levels measure only one aspect of renal function. Histologic evidence of incipient renal damage in such rats has been detected as early as the second day of the experiment (Hartroft; 1948). It is therefore obvious that more detailed studies of all aspects of renal function in these animals must be carried out before suggesting that the ocular hemorrhages may sometimes be unrelated to kidney damage.

The use of nephrectomized weanling rats possessing patent hyaloid arteries, so uniquely susceptible to hemorrhage, may prove of considerable value in investigations of the important relationship between renal dysfunction and ocular changes.

SUMMARY AND CONCLUSIONS

1. Confirming the work of previous investigators, ocular hemorrhages were found in weanling rats deprived of dietary choline. The incidence in our experiments varied from 35 percent to 85 percent of the animals, nearly all of which developed severe renal lesions.

2. All the hemorrhages but one (from the retina) in 209 eyes arose from the hyaloid arterial system. The mechanism appeared to be that of diapedesis rather than rhexis, at least in the early stages.

3. Morphologically identical hemorrhages were observed in bilaterally nephrectomized rats of the same age.

4. Neither deprivation of choline nor bilateral nephrectomy produced intraocular hemorrhages in older rats. Such rats do not develop such severe renal lesions on the choline-deficient diets, nor are their hyaloid arteries usually patent.

5. Of weanling rats whose blood levels of N.P.N. were determined at the time of occurrence of intraocular hemorrhage, 81 percent showed evidence of uremia. The remainder (7 rats) had intraocular hemorrhages in the presence of normal levels of nonprotein nitrogen in the blood.

6. Much of the evidence presented here suggests that the occurrence of intraocular hemorrhages in choline-deficient weanling rats is closely related to the coexistent, extensive renal damage.

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DISCUSSION

DR. A. B. REESE (New York City): Mr. Chairman, I know of one instance in which a severe vitreous hemorrhage occurred in an infant from a persistent hyaloid artery. The

question arose as to whether or not the condition was an intraocular tumor. It was elected to temporize, the hemorrhage absorbed, and the persistent hyaloid artery could be seen. We have a globe removed with the clinical diagnosis of tumor and microscopically no tumor was found. Instead, there was a massive vitreous hemorrhage from a persistent hyaloid artery.

DR. DAVID G. COGAN (Boston, Massachusetts): It seems to me that Dr. Kinsey's studies on the blood-aqueous barrier of young rabbits bears on the essayist's observations. Using ascorbic-acid transfer as an index, Dr. Kinsey found there was a much freer communication between the blood and aqueous humor when the hyaloid system was present than after its resolution.

DR. PARKER HEATH (Boston, Massachusetts): I would like to ask a question, if any of these animals were carried on to their ultimate conclusion, what happened to the hemorrhage? If there was a large volume of hemorrhage, what happened to the eyes?

DR. JONAS S. FRIEDENWALD (Baltimore, Maryland): I am very glad to hear from Dr. Reese that he has seen an actual case of intraocular hemorrhage arising from the hyaloid vessels.

I can't agree with Dr. Burns that the peculiar anatomy of the hyaloid system renders it abnormally susceptible to hemorrhage, at least not in human beings. In a large series of ours from stillborn human beings, we have found intraocular hemorrhages of various sizes in something like 20 percent of the routine sections.

Those hemorrhages have been almost exclusively in the retina and choroid, and out of several hundred cases I have yet to find a hemorrhage arising from a hyaloid system so that as compared with the other vessels in the eye, the hyaloid vessels do not break as easily under the stress of labor, in prematurity as do the other intraocular vessels.

DR. BURNS (closing): Dr. Reese's observations are very interesting to me. I haven't made much of an effort to correlate our findings with those in man. That ties in probably with what Dr. Friedenwald was saying. I don't know, but I would like to know, if, in the eyes Dr. Friedenwald was mentioning, the hyaloid arteries were patent.

DR. FRIEDENWALD: These were premature stillborns with hyaloid arteries.

DR. BURNS: I see. In these rats, as I mentioned, the hyaloid artery does persist into adult life but it is not patent and we felt that if it had been patent, bilateral nephrectomy would have caused intraocular hemorrhage.

As for the question about the ascorbic-acid transfer, I am afraid I am not a nutritionist and whatever I have included in the paper on nutrition has been second-hand from the experts in our department; so I can't make any further comment on that.

Regarding the ultimate fate of these animals, weanling rats on these choline-deficient diets die in from 7 to 10 to 12 days, depending on various factors. There are a few survivors. We had, out of 63 animals, 4 survivors in one experiment, if I remember the figure. Those animals had no intraocular hemorrhage.

Adult rats, if they are fed choline-deficient diets for a prolonged period, will survive for many months. They do have renal lesions but these renal lesions occur more slowly than in the weanlings, and there is apparently time for a repair process to take place, which means that they don't die from the renal lesions. They do, however, go on to cirrhosis of the liver from the piling up of fat there.

I don't know just how long they will survive, if nothing is done except feeding of choline-deficient diets. Dr. Hartroft has been doing some very interesting experiments, in which he has fed weanling rats diets deficient in choline for a period which, as closely as he could judge, was sufficient to produce renal damage of a very severe degree, but not quite enough to produce death; and subsequently switched them to normal diets and allowed them to grow to maturity. A great many of these animals developed hyperten-

sion when they became mature, especially in the case of females who became pregnant.*

We did find one animal in which I had examined the eyes ophthalmoscopically while it was on a choline-deficient diet, and it did have a fairly large hemorrhage in one eye, and that animal was allowed to survive; some three months later I examined the

* These findings have now been published. Hartroft, W. S., and Best, C. H.: Hypertension of renal origin in rats following less than one week of choline deficiency in early life. Brit. M. J., 1, 423 (Mar.) 1949.

same animal and found that hemorrhage was still present, although it had been absorbed to some extent, and there was a considerable amount of scarring present in the vitreous.

In the weanling rats, over short-time observations, that is from the time the hemorrhage occurred until the animal died, there was evidence that the hemorrhage was absorbed, particularly in the case of small hemorrhages. I couldn't say whether the larger hemorrhages were partially absorbed or not.

THE FATE OF TRANSPLANTED CILIARY-BODY TISSUE*

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The capacity of some types of tissue to survive when transplanted has brought about a considerable amount of experimental investigation and speculation. The object of this paper is to report in detail the results of transplanting pieces of normal, adult, homologous ciliary-body tissue in the rabbit. Sections were transplanted in the anterior chamber, under the bulbar conjunctiva, and subcutaneously. Histologic sections were made at periodic intervals and will be described subsequently.

One of the most spectacular workers in the field of tissue transplants was Voronoff[1] who attempted to prolong life and restore vital energy by transplanting testicular tissue experimentally in rams. He tried various locations in which to place his transplants: under the skin, intraperitoneally, and finally found the tunica vaginalis in the scrotum to be the most favorable site.

Voronoff made observations showing that

the youthful behavior of the old rams correlated with the histologic changes in the biopsies of the transplanted tissue. He noted that the seminiferous tubules of the graft continued for some time to form spermatozoa but that, little by little, the epithelium degenerated, the cells becoming changed into a syncytium containing numerous nuclei which filled the lumen of the tubules. This syncytium was then transformed, starting at the basement membrane, into a reticulated tissue. Depending on the size of the graft, these changes took place over a period of about 18 months. The significance of reporting Voronoff's work will be noted in the investigation which is to follow.

EXPERIMENTAL PROCEDURE

Two rabbits were anesthetized with 0.75 cc. of sodium pentothal (60 mg. per cc.) intravenously. The eyes to be operated were irrigated with zephiran (1:5,000).

Donor rabbit No. 1. An extensive corneal section was made at the limbus and following removal of the lens the iris and ciliary body were removed in toto and placed in a sterile petri dish containing normal saline. Under loupe magnification the ciliary body was easily separated from the iris. A small
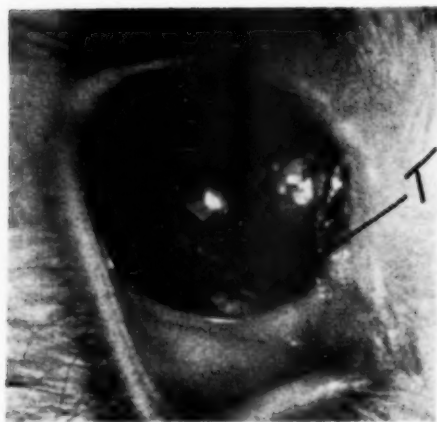
Fig. 1 (Danforth). Photograph of anterior chamber taken at the end of one month showing transplant attached to iris.

Fig. 2 (Danforth). Photomicrograph of normal rabbit ciliary-body tissue.

transplant, 2 by 3 mm., was then cut from this donor tissue.

Recipient rabbit No. 1. A conjunctival flap was made at the 11-o'clock position, followed by a keratome incision through the cornea. The prepared transplant tissue was then introduced into the anterior chamber

by manipulating it with iris forceps and an iris spatula. The conjunctival flap was then closed.

Observations. A small amount of hemorrhage in the anterior chamber was noted immediately following the above procedure. This cleared on the third day and at the end of the week the transplanted tissue had moved to the 12-o'clock meridian and appeared to be floating free in the anterior chamber. On the ninth day the tissue appeared to be attached to the anterior surface
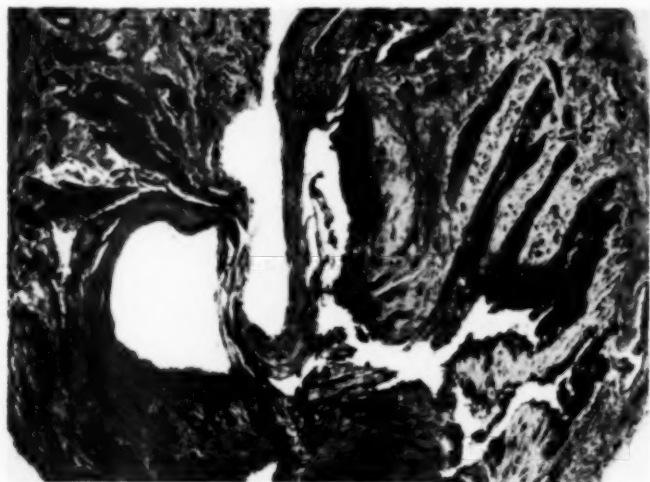
Fig. 3 (Danforth). Photomicrograph of section of transplant showing viable tissue with dilated capillaries, migration of pigment through stroma, and beginning atrophy of epithelial cells.

of the iris and was developing a pinkish, translucent color.

At the end of a month an iridectomy was performed removing the section of iris with the transplant for histologic study (figs. 1, 2, and 3).

Donor ciliary body tissue was again prepared as before. This time 0.1 of a unit of curare was added to the sodium pentothal, as advocated by Kirby and Hughson.[2] This practically eliminated the "whipping" which is apt to occur during the excitement stage, and from which one of the previous rabbits was lost from a broken back.

Pieces of ciliary-body tissue were then placed into the anterior chambers of four rabbit eyes in the same manner as previously described, except they were placed in different locations in the anterior chamber, two of them being placed over the pupillary area. A transplant was also made under the
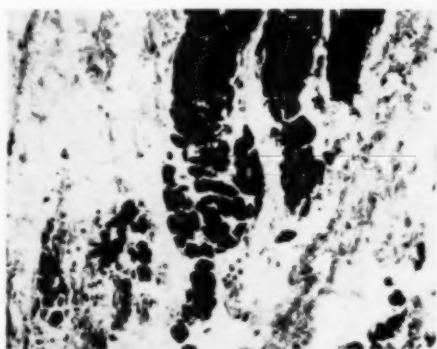
Fig. 4 (Danforth). Photomicrograph of section of subconjunctival transplant after one month, showing disintegration of transplant tissue with a few remnants of pigment.

bulbar conjunctiva and subcutaneously in one rabbit.

Observations of the transplants in the anterior chamber were the same as in the ini-
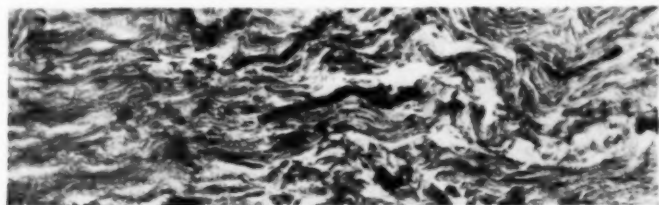
Fig. 5 (Danforth). Photomicrograph of subcutaneous transplant. There is almost complete dissolution of tissue.
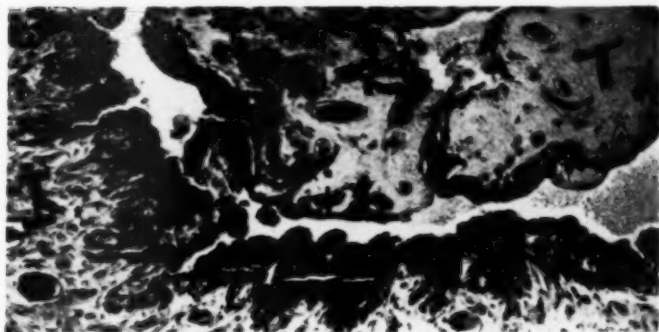
Fig. 6 (Danforth). Photomicrograph of transplant (T) in anterior chamber after two months. The tissue is still viable. There is wider dilatation of the capillaries and further atrophy of epithelial cells. (I) iris.

Fig. 7 (Danforth). Photomicrograph of section at six months shows: (A) Cornea, (B) transplant, (C) iris. Section reveals (1) Transplant is attached to iris; (2) there is local dilatation of vessels of the iris in the region of the transplant; (3) only a few attenuated capillaries in the transplant which are nearly empty of blood; (4) cells have nearly lost their identity, appear like a syncytium; (5) epithelial cells can no longer be identified.
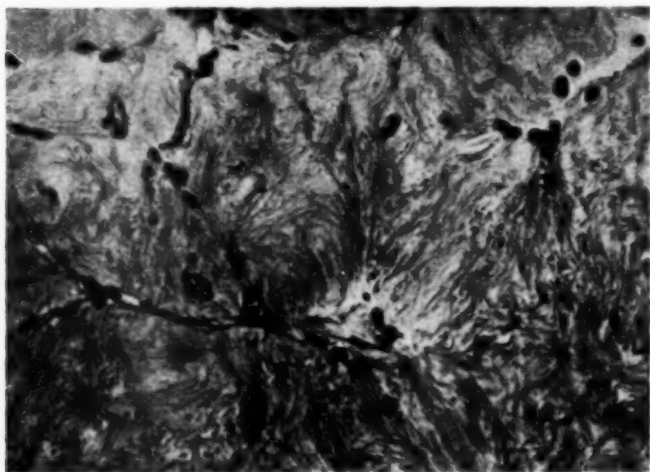
Fig. 8 (Danforth). High-power photomicrograph of the transplant in Figure 7.

tial recipient rabbit. It was noted, however, that during the first week there was a migration of the transplants placed over the pupillary areas to the anterior surface of the iris. They all appeared pink and viable by the 8th to 9th day.

At the end of a month a biopsy was made in the region of the transplants, which were under the skin and conjunctiva. Iridectomies were performed, removing for histologic study a segment of iris and attached ciliary body tissue at the end of 2 months, 5 months, and 6 months (figs. 4, 5, 6, 7, and 8). From the 2nd month until the 6th month there appeared to be a gradual shrinkage and increasing pallor of the transplants on gross inspection.

DISCUSSION

Strangely enough the anterior chamber of the eye as a site for tissue transplants has been extensively exploited, not by ophthalmologists, but by cancer research workers. Greene,[3] whose extensive and painstaking work has been so well summarized by Blake,[4] found that not only was the anterior chamber of the eye the only place where he could cause malignant tissue transplants to survive but that the cornea acted as a window so that he could study the transplants under magnification at any desired interval without disturbing the transplant. He was mainly interested in finding a laboratory animal in which he could grow human cancer tissue and he found that malignant-tumor tissue would not only survive, but that it could be retransplanted in such animals as the rabbit or guinea pig.

Greene also reported that human embryonic tissue would survive and grow in the anterior chamber of the eyes of these animals but that benign-tumor tissue and, with the exception of skin and cartilage, normal-adult tissue would not survive. He also tried transplanting tissue sections from the various endocrine glands and met with constant failure.

We recently transplanted a small piece of tissue from a retinoblastoma into the anterior chamber of a rabbit which failed to survive. There is, however, a very good possibility that the tissue we received was necrotic before removal.

It would be logical to reason that the present work being done by transplanting pieces of placental tissue subcutaneously as advocated by Filatov[5] could have but the same fate as the gonad transplants of Voronoff and the ciliary body. However, there could well be absorption of products during disintegration of these transplants, as was the case with Voronoff's rams, which, by repeated transplants at proper intervals, would make this procedure worth while.

SUMMARY

1. Sections of ciliary-body tissue from the rabbit were transplanted into the anterior chamber, subcutaneously and subconjunctivally, of another rabbit.

2. Periodic histologic sections were taken of the transplants in the anterior chamber up to a period of 6 months for study.

3. Biopsies were taken of the tissue transplanted subconjunctivally and subcutaneously after a period of one month which showed nearly complete absorption of transplanted tissue.

4. In the transplanted tissue in the anterior chamber there was attachment to the iris formed in about a week with dilatation of the capillaries. There was, however, a progressive atrophy of the epithelial tissue and stroma until finally the whole mass appeared to be replaced by a fibrous tissue-appearing syncytium.

5. These observations confirm the work of Voronoff and Greene on the failure of normal, adult, homologous tissue of this type to survive when transplanted.

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EFFECTS OF TESTICULAR EXTRACT ON CERTAIN OCULAR STRUCTURES*

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Introduction

Morphologists have appreciated for many years that the fibrous intercellular substances of connective tissue (collagenic, reticular, and elastic fibers) are associated in many parts of the body with nonfibrous jellylike materials. Moreover, they have appreciated that these jellylike materials, commonly called ground or cement substances, are relatively abundant in the tissues of the fetus, and that aging is associated with a decrease in the ratio of jellylike types to fibrous types.

In general, however, the nonfibrous intercellular substances have received little attention and it is only since the relatively recent researchers of Meyer and his associates that they have come to be viewed in a proper perspective. It has become apparent that, in general, the so-called ground or cement substances are mucopolysaccharides—substances of great molecular weight.[1] What is generally termed ground substance is a nonsulphated type of mucopolysaccharide, called *hyaluronic acid*,[2] a composite word from hyaline, meaning glassy or clear, and glucuronic acid of which it is partly composed. Many of the so-called cement substances are sulfated types of mucopolysaccharide.[1]

In sections, the two types may usually be differentiated from one another by their staining reaction with metachromatic dyes.[3] The sulfated types usually take on a different color from that of the dye, for example with toluidene blue they become colored purple or red.

The physical state, and hence the fluidity, of hyaluronic acid differs in different parts of the body. That of the aqueous humor is 95 percent depolymerized.[1] That of ordinary connective tissue, however, is probably highly polymerized and jellylike in consistency. The sulfated mucopolysaccharides commonly exist in the body as firm gels of which the hyaluronic acid sulfate of the cornea and the chondroitin sulfuric acid of cartilage are examples.[1]

Meyer has shown that testicular extracts contain an enzyme that brings about the depolymerization of hyaluronic acid.[1] Hence it has been termed *hyaluronidase*. Either this or other enzymes associated with it in testicular extracts effect the breakdown of sulfated mucopolysaccharides also, but this reaction occurs relatively slowly.[4]

The depolymerization of hyaluronic acid by hyaluronidase affects both its diffusibility and its osmotic pressure. Since the hyaluronic acid of the aqueous is largely depolymerized, and since hyaluronidase has been recovered from macerations of iris and ciliary body[5] and from aqueous,[6] it might be suspected that some normal mechanism operates in the eye both to produce and depolymerize hyaluronic acid. Accordingly, it was thought of interest to investigate the effects on the eye of giving large amounts of hyaluronidase to animals over considerable periods of time.

Methods

Testicular extract was prepared by the method first described by Madinaveitia.[7] A 50-percent to 100-percent fraction was diluted to 60 turbidity reducing units per cc., sterilized by Seitz filtration, bottled, and refrigerated until used.

One cc. was injected into each of four

6-month-old rabbits and four 2-year-old guinea pigs, twice daily, both intraperitoneally and subcutaneously, for from 20 to 55 days. Two of the guinea pigs and one rabbit given 55 daily injections were allowed a 30-day recovery period before being killed; the others were all killed the morning after their last injection. Eyes were enucleated just before the animals died from ether anesthesia.

Each eye was immersed in formol-saline for 5 minutes in order to harden it slightly before a window was cut in its cornea and sclera to permit of more rapid fixation. After 24-hours' fixation the eyes were dehydrated and embedded in paraffin. Alternate sections were stained with hematoxylin and eosin and with toluidene blue.

In addition to the foregoing material some sections were obtained from normal eyes that were subjected to the action of testicular extract after death as follows:

Two 6-week-old rabbits were killed with ether. A very small opening was then cut in the cornea of each eye. A hypodermic needle was then passed through the sclera near the limbus into the posterior chamber and 2 cc. of testicular extract were slowly perfused under slight pressure into one eye of each animal, great care being taken not to dislocate the lens. Boiled testicular extract was similarly injected into the other eye of each animal. After 30 minutes at room temperature, the eyes were enucleated and sectioned in the same manner as the others.

Observations

The chief morphologic changes that occurred in the experimental animals were found in their anterior ciliary processes. These structures in the normal rabbit are, according to our observations, of two general types, which differ from each other chiefly by the extent and character of their stroma.

Those of the first type are stout (fig. 1) and possess an abundant content of a primitive type of connective tissue which contains star-shaped cells, widely separated by an intercellular substance which stains only very faintly with eosin and is not metachromatic with toluidene blue.

The second type of anterior ciliary process is thin and contains only a scanty amount of a more condensed type of intercellular

Fig. 1 (MacDonald). Normal anterior ciliary process of the stout type in the rabbit. Note the watery nature of the intercellular substance.

substance which stains with eosin, and is metachromatic with toluidene blue.

In sections of the eyes that were injected with testicular extract after death, the most striking change is that the intercellular substance of the stout variety of anterior ciliary processes has almost disappeared leaving only capillaries and concentrations of connective tissue cells (fig. 2). The ciliary processes of the eyes injected with inactivated extract are still stout and contain their intercellular substance.

The stout type of anterior ciliary process becomes changed in those rabbits given testicular extract for long periods of time. The change essentially is a substitution of a
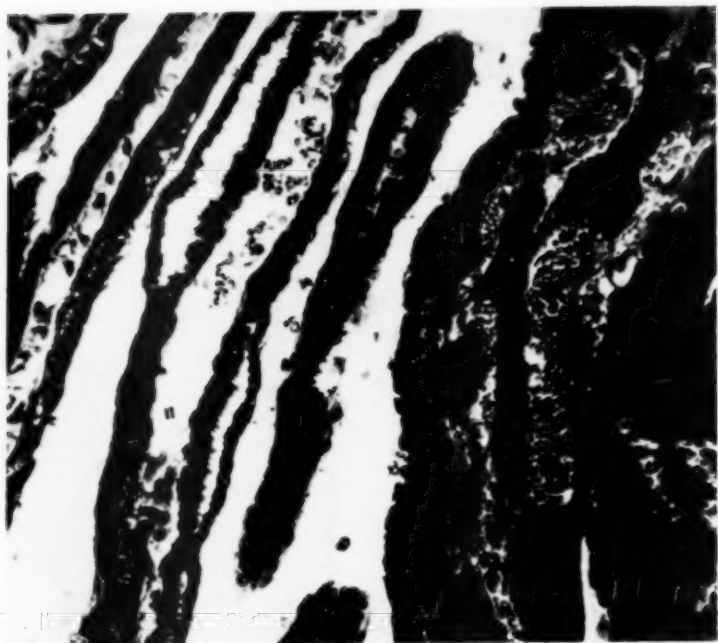
Fig. 2 (MacDonald). Anterior ciliary process after exposure to testicular extract in vitro. Note loss of intercellular substance and partial separation between epithelial layers.

Fig. 3 (MacDonald). Anterior ciliary process after prolonged administration of testicular extract. Note more solid nature of the intercellular substance. Iris is at right, lens at left.

more solid type of intercellular substance of an amorphous character that stains with eosin, and is metachromatic with toluidene blue (fig. 3), for the more fluid and more poorly staining intercellular substance observed in the normal process. In the rabbits allowed a 30-day recovery period after the injections of extract ceased, the altered intercellular substance in the process still persists.

The eyes of guinea pigs possess anterior ciliary processes of a considerably different type from those observed in the rabbit and no change is observed in the intercellular substance of the cores of those of the animals given testicular extract for long periods of time. A change, however, is observed in that the two epithelial layers covering the ciliary body and processes are almost completely separated from each other in the instance of two eyes (fig. 4) and partially separated in two others. No such separation is observed in the eyes of control guinea pigs fixed and sectioned in the same manner.

An additional lesion in the rabbits given testicular extract for long periods of time was observed in the extraocular muscles. These exhibit a patchy distribution of lesions that were of a combination of muscle

Fig. 5 (MacDonald). Extraocular muscle lesion in the rabbit after prolonged administration of testicular extract.

degeneration and cellular proliferation. The latter involves both the endomysium of the muscles and the muscle fibers themselves. In some sites the lesions are associated with a mild infiltration of mononuclear cells (fig. 5).

DISCUSSION

The fact that the intercellular substance of the stout type of anterior ciliary process of the normal rabbit's eye appears in sections to be of a more or less fluid nature, and does not stain with eosin, and is not metachromatic with toluidene blue, suggests that it is hyaluronic acid. The fact that it dissolves away in the instance of eyes injected with testicular extract after death is confirmatory evidence to this effect.

The fact that the intercellular substance of the ciliary processes of the eyes of the rabbits given testicular extract for long periods of time became of such a character that it stained with eosin and was metachromatic with toluidene blue suggests that a sulfated type of mucopolysaccharide be-

Fig. 4 (MacDonald). Separation of epithelial layers of guinea pig following prolonged administration of testicular extract.

came substituted for hyaluronic acid under the conditions of the experiment.

It is difficult to assess the significance of this finding. It is tempting to suggest that this provides evidence of hyaluronidase injected at one site in the body having a pronounced effect at another. But the extract was a relatively wide-range fraction probably containing protein, and hence the possibility of the changes in the ciliary processes being of the nature of a foreign-protein response must be taken into account.

It is of interest that aging is known to be associated with changes in the quality of the intercellular substances of the ciliary processes which are in general in the character of what might be termed a solidifying nature[8] and hence somewhat similar to those obtained in this experiment.

The separation of the layers of epithelium observed in the ciliary processes of the guinea pigs given extract for long periods of time also suggests an effect on the cement substances at a site distant from that of the injection.

Although no precise information is available about the nature of the cement substance assumed to hold these two layers of epithelium together, it is not unlikely that it, like other cement substances, is of the nature of a sulfated mucopolysaccharide. The extract used in this experiment contains, as noted previously, enzymes that react with this type of intercellular substance as well as with hyaluronic acid.

The lesions seen in the extraocular muscles were similar to those found in many other striated muscles of the experimental animals. The nature and cause of the muscle lesion is being investigated in collaboration with other members of the department in which this work was done and who are interested in the effects of hyaluronidase in sites other than the eye.

It may be said, however, that the muscle lesion is not unlike that seen in biopsies of muscle obtained from certain stages of some types of rheumatic diseases. The fact that certain investigators have reported the production of muscle lesions as a result of the injection of foreign protein,[9] however, makes it unwise at this time to attribute the muscle lesion to the enzymes of the extract acting on a substrate in the muscle. Further work will be necessary before any conclusions can be drawn on this matter.

SUMMARY

Two types of ciliary processes were found in the 6-month-old rabbit, a thick and a thin type. The thick type contains a primitive form of connective tissue not unlike that found in umbilical cord. After the thick type is subjected to the action of testicular extract for 30 minutes it loses most of its intercellular substance. This, as well as its morphologic characteristics, suggests that it is hyaluronic acid.

On the other hand, in rabbits injected with testicular extract over long periods of time, the intercellular substance of the thick type of process becomes denser and stains metachromatically. This suggests that hyaluronic acid is here replaced by a sulfated type of mucopolysaccharide under the experimental procedure.

In guinea pigs similarly treated over long periods, the two epithelial layers covering the ciliary body become separated. Also degenerative and proliferative lesions of the extraocular muscles develop in the rabbits injected with testicular extract.

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DISCUSSION

DR. JONAS S. FRIEDENWALD (Baltimore, Maryland): I think that Dr. MacDonald has opened a very interesting and fascinating subject, and I am very glad indeed that he has started to work in this field. What I wanted to ask him was whether he was aware of the technique of Hotchkiss for mucoid stain with the aid of which one can settle some of the problems about which he seems to be in doubt. This Hotchkiss technique is a general stain for mucoids of a much more highly specific character than the faint color difference which one gets with the metachromatic stain and one can stain tissues and see where the mucoids are, and one can take parallel sections and expose them to various enzymes such as hyaluronidase and see whether certain mucoids disappear and thus can identify quite well which mucoids were present.

DR DAVID G. COGAN (Boston, Massachusetts): I would be interested to know what changes other than those in the ciliary body occur.

DR. ERNST SCHMERL (Toledo, Ohio): May I ask whether the ocular tension was affected by the administration of the testicular extract?

DR. MACDONALD (closing): In answer to Dr. Friedenwald's question, we have tried Hotchkiss's technique of staining for hyaluronic acid without very much success, because the ground substance disappeared in our in vitro experiments in which hyaluronidase was acting on the tissues. This along with its other staining qualities led us to believe it was hyaluronic acid. The reason that most of our observations on the eye concerned the anterior ciliary processes in rabbits was because of the simplicity of the primitive type of connective tissue there.

We looked for changes elsewhere but because of complexity of the tissues we were not able to make any definite observations.

In regard to changes in ocular tension, we were not able to establish definitely any changes in intraocular pressures, although we did find changes in the rate of diffusibility of fluorescein using ultraviolet light. Our present experiments involve a much larger series and half these animals demonstrate rapid diffusibility of fluorescein in the aqueous as compared with the normal. It comes in great clouds.

We really have not done enough control animals to know just what the normal range is.

THE USE OF ALKYL-DIMETHYL-BENZYL AMMONIUM CHLORIDE FOR MAINTENANCE OF STERILITY IN SOLUTIONS*

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Experimental eye surgery on rabbits has several hazards, one of which is postoperative infection. While doing experimental eye surgery it was found on two occasions that the particular organism responsible could be traced to one of the solutions used in connection with the operation. In doing animal work it would be convenient to have freshly autoclaved solutions. However, this is not always possible so that it was deemed worth while to investigate a method whereby the solutions used in experimental ophthalmic surgery could be kept sterile for a reasonable length of time. It also seemed that, if this method were successful, it could be used to keep solutions ordinarily used in ophthalmology sterile for longer periods.

Alkyl-dimethyl-benzyl ammonium chloride solution, known by its trade name Zephiran chloride, seemed a suitable bactericidal agent because it is compatible with all drugs used in ocular surgery except eserine salicylate. It is, however, compatible with eserine sulphate. It has been shown by Domagk[1] and Walter[2] to be nontoxic when given to animals internally and also to be noninjurious in the conjunctival sac of human beings in concentrations of 1:1,000 to 1:5,000. It has been used to maintain the sterility of vaccines by Maier,[3] and has been shown to be an efficient bactericide by the work of Dunn,[4] Hoyt, Fisk, and Burde,[5] also Heineman[6] and Thompson.[7] This chemical has been shown to be suitable for ocular use by

O'Brien.[8] It also has the advantage of being thermostabile as was demonstrated by Dunn.[9] Sevag and Ross[10] used it as a fungicide and Dunn[11] also used it against molds.

In order to test further the toxicity of this chemical agent, the aqueous of one eye of each of three rabbits was replaced by Zephiran chloride in saline in a concentration of 1:3,000, 1:6,000, and 1:7,500. The aqueous of the fellow eye of these animals was replaced by normal saline. In three animals in which the 1:3,000 solution was used, and the three animals in which the 1:6,000 solution was used, endothelial edema was caused which, however, disappeared in from 6 to 8 weeks. The degree of edema was in direct proportion to the concentration of the solution. In three animals in which the aqueous was replaced by a saline solution of Zephiran chloride in a concentration of 1:7,500, no visible evidence of damage could be ascertained with a hand slitlamp.

At the time this work was done we were unaware of the work of Post.[12] Post did very much the same type of experiment but used concentrations of Zephiran chloride of 1:500, 1:1,000, and 1:3,000, and stated that there was necrosis of the iris in all of these concentrations.

PROCEDURE

In order to simulate actual conditions, but to an exaggerated degree, the following drugs were dissolved in an aqueous solution of Zephiran chloride of 1:5,000: atropine sulphate (1 percent), pilocarpine (1 percent), pontocaine (0.5 percent), fluorescein (2 percent), eserine sulphate (0.5 percent). These solutions were placed in bottles such as are

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ordinarily used for containing ophthalmic solutions, and were capped with rubber stoppers which were held in place by bandages. As a control to test and compare the efficacy of Zephiran chloride the drugs mentioned above were dissolved in triple-distilled water, and capped in similar manner. All the solutions were then autoclaved in the bottles. The bottles had a capacity of 60 cc. The opening was one centimeter in diameter.

Twelve hours later the rubber stoppers were removed from the bottles, samples of the drugs were taken immediately, and cultured in bacteriologic culture media to test the sterility of the solutions. The bottles were allowed to stand open in the laboratory, unprotected for 19 days. Samples were taken subsequently after 1, 7, 14, and 19 days from each of the bottles and inoculated in liquid media in tubes. Several different media were used. These will be described subsequently.

The inoculations were done in quadruplicate and the inoculated tubes were incubated aerobically and anaerobically, both at 37°C. and room temperature. The room temperature during the time of the experiment ranged from 16°C. to 24°C. (60° to 75°F.).

After 3 to 5 days, the cultures were examined macroscopically and any gross changes in the media noted. Smears were made from each tube. These were stained by Gram's method and examined. Whenever bacteria were observed in the smears the different morphologic types, their Gram reaction, and their relative number were recorded. No further identification was attempted.

The final experimental procedure was the subculturing of each of the primary cultures. This was done by preparing agar pour plates. Approximately 0.5 cc. of the primary culture was used to inoculate these plates. The pour plates were incubated aerobically at 37°C. for 5 days and examined daily for the presence or absence of bacterial colonies. In most cases where colonies were present, representative colonial forms were selected, smears were made, stained by Gram's

method, and examined. Except for the unstoppered bottles of the drugs, aseptic technique was observed throughout the experimental procedure.

The volume of drug tested each time was 0.5 cc. in 7 cc. of medium. The volume of the medium was such that culture tubes 6 by ⅝ inches could be used. This was an advantage as all of the tubes at any one sampling interval could be placed in four anaerobic jars and incubated anaerobically. This ratio gave a final dilution of Zephiran chloride of 1:75,000 in each tube. This dilution was considered to be sufficiently high so as not to exert any bacteriostatic or bactericidal effect during the period of incubation. However, as a control of bacteriostasis, the primary cultures, as stated in the preceding paragraph, were always subcultured.

Dunn[4] reported the dilution ratios of Zephiran chloride capable of destroying various organisms in 10 minutes but not in 5 minutes at 20°C. and at 37°C. With the exception of a strain of Hemolytic streptococcus, which was destroyed by a solution of Zephiran chloride 1:95,000 at 20°C., the species of bacteria and cryptococcus which he tested were destroyed by a dilution of 1:70,000 or less.

Using a Gram-positive and a Gram-negative organism, we tested the action of Zephiran chloride in a dilution of 1:75,000 in sterile evaporated milk. Two-mm. loopfuls of a broth culture of Staphylococcus aureus and of E. coli were inoculated at 37°C. and at room temperature for 24 hours. At the end of this time, the growth was abundant in all four tubes. It may be mentioned now, but referred to later, that in parallel tests with blood broth Staphylococous aureus failed to grow in the broth plus Zephiran, both at 37°C. and at room temperature. The strain of E coli appeared to grow equally as well in the broth with Zephiran as in the broth without Zephiran.

The media used for testing the sterility of the drugs were whole evaporated milk and

TABLE 1*

ATROPINE SULFATE (1 PERCENT) IN ZEPHIRAN (1:5,000)†

Intervals of Sampling	Media for Primary Culture Kind	pH	Explanation of Observations Columns 4 to 5		Zephiran 1:5,000 Aerobic 37°C	R.T.	Anaerobic 37°C	R.T.	Organisms in Smears Line 2	Sterile Distilled Water Aerobic 37°C	R.T.	Anaerobic 37°C	R.T.	Organisms in Smears Line 2
Col. 1	Col. 2		Col. 3		Col. 4					Col. 5				
Imm.	Whole Evap. Milk	5.90	*Line 1* Macroscopic change noted in primary culture after 2–5 days incubation (primary cultures =0.5 cc. of solution in 7 cc. of medium)	1	−	−	−	−		−	−	−	−	
				2	−	−	−	−		−	−	−	−	
				3	−	−	−	−		−	−	−	−	
	Rabbit Blood Neopep. Broth	7.20		1	−	−	−	−		−	−	−	−	
				2	−	−	−	−		−	−	−	−	
				3	−	−	−	−		−	−	−	−	
1 Day	Whole Evap. Milk	5.90		1	−	−	−	−		−	−	−	−	
				2	−	−	−	−		−	−	−	−	
				3	−	−	−	−		−	−	−	−	
	Rabbit Blood Neopep. Broth	7.20		1	−	−	−	−		−	−	−	−	
			Line 2 Smears of primary culture stained by Gram's method.	2	−	−	−	−		−	−	−	−	
				3	−	−	−	−		−	−	−	−	
7 Days	Whole Evap. Milk	5.90		1	−	−	−	−						
				2	−	−	−	−		PC	PC	−	−	Gr. +rods (2 types) Gr. +cocci.
				3	−	1ª	−	−		4 +	3 +	2 +	4 +	
										4 +	4 +	4 +	4 +	
	Rabbit Blood Neopep. Broth	7.20		1	−	−	−	−		T	T	T	−	Gr. +rods (2 types) Gr. +cocci. and molds
				2	−	−	−	−		4 +	3 +	4 +	±	
				3	1ª	−	−	−		4 +	4 +	4 +	4 +	
14 Days	Whole Evap. Milk	5.90		1	−	−	−	−		−	−	−	−	Gr. +rods (1 type)
				2	−	−	−	−		4 +	3 +	±	±	
			Line 3 Colonies present in pour plates made of primary culture after 2–5 days incubation. (Pour plates were incubated aerobically at 37°C.)	3	−	−	−	−		4 +	4 +	4 +	4 +	
	Whole Evap. Milk	5.90		1	−	−	−	−		−	−	−	−	Gr. +rods (1 type)
				2	−	−	−	−		4 +	4 +	4 +	4 +	
				3	−	2ª	−	−		4 +	4 +	4 +	4 +	
19 Days	Dil. Evap. Milk	7.00		1	−	−	−	−		−	−	−	−	Gr. +rods. (1 type)
				2	−	−	−	−		3 +	3 +	±	±	
				3	−	−	−	−		4 +	4 +	2 +	2 +	
	Dil. Evap. Milk	7.00		1	−	−	−	−		−	−	−	−	Gr. +rods (1 type)
				2	−	−	−	−		3 +	3 +	±	±	
				3	−	−	−	−		4 +	4 +	2 +	2 +	
	Rabbit Blood Neopep. Broth	7.20		1	−	−	−	−		T	T	T	T	Gr. +rods (1 type)
				2	−	−	−	−		±	±	±	±	
				3	−	−	−	45ᵇ		4 +	4 +	2 +	2 +	

*EXPLANATION OF SYMBOLS IN TABLES

Imm.: immediately
Whole evap. Milk: whole evaporated milk
Dil. Evap. Milk: diluted evaporated milk
Rabbit Blood Neopep. Broth: rabbit blood neopeptone infusion broth
R.T.: room temperature
LINE 1
　Minus sign: no macroscopic change in the primary culture
　C: coagulation
　PC: partial coagulation
　T: turbidity
LINE 2
　Minus sign: no microörganisms seen in the smear of the primary culture stained by Gram's technique
　Plus over minus to 4 plus: the relative numbers of microörganisms seen in the smears of the primary cultures stained by Gram's technique
LINE 3
　Minus sign: no colonies in the pour plates made of the primary cultures.
　Plus over minus to 4 plus: the relative number of colonies in the pour plates. When the number of colonies per plate is 100 or less the exact number is recorded.
　pH of the primary cultures after inoculation with the solutions:

Whole Evap. milk plus atropine sulfate in Zephiran	=5.90
Whole Evap. milk plus atropine sulfate in distilled water	=5.90
Rabbit Blood Neopep. Broth plus atropine sulfate in Zephiran	=7.18
Rabbit Blood Neopep. Broth plus atropine sulfate in distilled water	=7.20

† Sterile distilled water was used. Solutions and media were sterilized by autoclaving.
ª Colonies are probably surface contaminants.
ᵇ Molds.

TABLE 2*

ESERINE SULFATE (0.5 PERCENT) IN ZEPHIRAN (1:5,000)†

Intervals of Sampling	Media for Primary Culture		Explanation of Observations Columns 4–5		Zephiran 1:5,000					Sterile Distilled Water				
					Incubation of Primary Culture				Organisms in Smears Line 2	Incubation of Primary Culture				Organisms in Smears Line 2
					Aerobic		Anaerobic			Aerobic		Anaerobic		
	Kind	pH			37°C	R.T.	37°C	R.T.		37°C	R.T.	37°C	R.T.	
Col. 1	Col. 2		Col. 3		Col. 4					Col. 5				
Imm.	Whole Evap. Milk	5.90	*Line 1* Macroscopic change noted in primary culture after 2–5 days incubation (primary cultures =0.5 cc. of solution in 7 cc. of medium)	1 2 3	– – –	– – –	– – –	– – –		– – –	– – –	– – –	– – –	
	Rabbit Blood Neopep. Broth	7.20		1 2 3	– – –	– – –	– – –	– – –		– – –	– – –	– – –	– – –	
1 Day	Whole Evap. Milk	5.90		1 2 3	– – –	– – –	– – –	– – –		– – –	– – –	– – –	– – –	
	Rabbit Blood Neopep. Broth	7.20		1 2 3	– – –	– – –	– – –	– – –		– – –	– – –	– – –	– – –	
7 Days	Whole Evap. Milk	5.90	*Line 2* Smears of primary culture stained by Gram's method.	1 2 3	– – –	– – –	– – –	– 1ᵃ –		– – –	– 1ᵇ –	– 1ᵇ –	– – –	
	Rabbit Blood Neopep. Broth	7.20		1 2 3	– – –	– – –	– – –	– – –		– – –	– – –	– – –	– – 4ᶜ	
14 Days	Whole Evap. Milk	5.90		1 2 3	– – –	– – –	– – –	– – –		– – 3ᶜ	– – –	– – –	– – –	
	Whole Evap. Milk	5.90	*Line 3* Colonies present in pour plates made of primary culture after 2–5 days incubation. (Pour plates were incubated aerobically at 37°C.)	1 2 3	– – –	– – –	– – –	– – –		– – 4	– – –	– – –	– – –	
19 Days	Dil. Evap. Milk	7.00		1 2 3	– – –	– – –	– – –	– – –		– – –	– – –	– – 1ᵈ	– – 60ᵈ	
	Dil. Evap. Milk	7.00		1 2 3	– – –	– – –	– – –	– – –		– – –	– – –	– – 2ᵈ	– – 1+ᵈ	
	Rabbit Blood Neopep. Broth	7.20		1 2 3	– – –	– – –	– – –	– – –	— — —	– – –	– – –	– – –	T — 4+ᵈ	

* See * of Table 1 for explanation of symbols.
† Sterile distilled water was used. Solutions and media were sterilized by autoclaving.
ᵃ Mold, surface contaminant.
ᵇ Opaque white surface colonies (Gram +cocci). Probably surface contaminants.
ᶜ Opaque yellow surface colonies (Gram +cocci). Probably surface contaminants.
ᵈ Subsurface colonies (Gram +rods).

evaporated milk diluted with equal parts of neopeptone infusion broth and 5-percent rabbit blood neopeptone infusion broth. The pH of the whole evaporated milk was not adjusted. After autoclaving it was found to have pH of 5.90. The pH of the diluted evaporated milk and of the blood broth was adjusted so as to be between pH 7.0 to pH 7.2 after autoclaving. Toward the end of the experiment, because of the viscosity of the whole evaporated milk, the diluted milk was used as a substitute. The diluted milk not only facilitated a more uniform mixing of drugs and media, but it also insured more accurate measurement of the volume of the culture used in the agar pour plates.

The evaporated milk was considered to be a better medium for this work than the blood broth, since McCulloch[13] reported that false disinfection velocity curves are produced by quaternary ammonium compounds, of which group Zephiran chloride is a member. He found that sterile evaporated milk allowed the growth of organisms exposed to solu-

TABLE 4*

PILOCARPINE (1 PERCENT) IN ZEPHIRAN (1:5,000)†

Intervals of Sampling	Media for Primary Culture		Explanation of Observations 4 Columns 4-5		Zephiran 1:5,000					Sterile Distilled Water				
					Incubation of Primary Culture				Organisms in Smears Line 2	Incubation of Primary Culture				Organisms in Smears Line 2
					Aerobic		Anaerobic			Aerobic		Anaerobic		
	Kind	pH			37°C.	R.T.	37°C.	R.T.		37°C.	R.T.	37°C.	R.T.	
Col. 1	Col. 2		Col. 3		Col. 4					Col. 5				
Imm.	Whole Evap. Milk	5.90	*Line 1* Macroscopic change noted in primary culture after 2-5 days incubation (primary cultures =0.5 cc. of solution in 7 cc. of medium)	1 2 3	— — —	— — —	— — —	— — —		— — —	— — —	— — —	— — —	
	Rabbit Blood Neopep. Broth	7.20		1 2 3	— — —	— — —	— — —	— — —		— — —	— — —	— — —	— — —	
1 Day	Whole Evap. Milk	5.90		1 2 3	— — —	— — —	— — —	— — —		— — —	— — —	— — —	— — —	
	Rabbit Blood Neopep. Broth	7.20	*Line 2* Smears of primary culture stained by Gram's method.	1 2 3	— — —	— — —	— — —	— — —		— — —	— — —	— — —	— — —	
7 Days	Whole Evap. Milk	5.90		1 2 3	— — —	— — 2^b	— — 2^b	— — —		— — —	— — —	— — 1	— — 1^b	
	Rabbit Blood Neopep. Broth	7.20		1 2 3	— — 1^b	— — —	— — —	— — —		— — 30^c	— — $\pm/3^d$	— — 1^b	— — —	{Gr. +rods}
14 Days	Whole Evap. Milk	5.90	*Line 3* Colonies present in pour plates made of primary culture after 2-5 days incubation. (Pour plates were incubated aerobically at 37°C.)	1 2 3	— — —	— — —	— — —	— — —		— — —	— 1^b —	— — —	— — —	
	Whole Evap. Milk	5.90		1 2 3	— — —	— — —	— — —	— — —		— — —	— — —	— — —	— — —	
	Dil. Evap. Milk	7.00		1 2 3	— — —	— — —	— — —	— — —		— — —	— — —	— — —	— — —	
19 Days	Dil. Evap. Milk	7.00		1 2 3	— — —	— — —	— — —	— — —		— — —	— — —	— — —	— — —	
	Rabbit Blood Neopep. Broth	7.20		1 2 3	— — —	— — —	— — —	— — —		— — —	— — —	— $\pm$ $4+^e$	— — —	{Gr. +rods}

* See * of Table 1 for explanation of symbols.
† Sterile distilled water was used. Solutions and media were sterilized by autoclaving.
a Subsurface colonies (Gram +cocci). Probably contaminants.
b Opaque yellow and white surface colonies. (Gram +cocci). Probably contaminants.
c Subsurface and surface colonies of molds and bacteria. The bacteria are Gram +cocci and Gram +rods.
d Subsurface colonies (Gram +rods). Probably contaminants.
e Subsurface and grayish white, flat surface colonies (Gram +rods and Gram −rods).

method are in line 2 of columns 4 and 5, and the observations of the pour plates in line 3 of the same columns.

CONCLUSIONS

TABLE 1

Atropine sulphate (1 percent) dissolved in aqueous solution of Zephiran chloride remained sterile under conditions described for a period of 14 days to 19 days at which time the solution was contaminated by molds.

TABLE 2

Eserine sulphate (0.5 percent) in Zephiran chloride 1:5,000 remained sterile during the 19 days.

TABLE 5*

PONTOCAINE (0.5 PERCENT) IN ZEPHIRAN (1:5,000)†

Intervals of Sampling	Media for Primary Culture — Kind	pH	Explanation of Observations Columns 4-5	Obs	Zephiran 1:5,000 — Aerobic 37°C	R.T.	Anaerobic 37°C	R.T.	Organisms in Smears Line 2	Sterile Distilled Water — Aerobic 37°C	R.T.	Anaerobic 37°C	R.T.	Organisms in Smears Line 2
Col. 1	Col. 2		Col. 3		Col. 4					Col. 5				
Imm.	Whole Evap. Milk	5.90	*Line 1* Macroscopic change noted in primary culture after 2–5 days incubation (primary cultures =0.5 cc. of solution in 7 cc. of medium)	1	—	—	—	—		—	—	—	—	
				2	—	—	—	—		—	—	—	—	
				3	—	—	—	—		—	—	—	—	
	Rabbit Blood Neopep. Broth	7.20		1	—	—	—	—		—	—	—	—	
				2	—	—	—	—		—	—	—	—	
				3	—	—	—	—		—	—	—	—	
1 Day	Whole Evap. Milk	5.90		1	—	—	—	—		—	—	—	—	
				2	—	—	—	—		—	—	—	—	
				3	—	—	—	—		—	—	—	—	
	Rabbit Blood Neopep. Broth	7.20	*Line 2* Smears of primary culture stained by Gram's method.	1	—	—	—	—		—	—	—	—	
				2	—	—	—	—		—	—	—	—	
				3	—	—	—	—		—	—	—	—	
7 Days	Whole Evap. Milk	5.90		1	—	—	—	—		—	—	—	—	
				2	—	—	—	—		1ᵃ	—	2 +ᵈ	—	
				3	—	—	—	—		—	—	—	—	
	Rabbit Blood Neopep. Broth	7.20		1	—	—	—	—		—	—	—	—	
				2	—	—	—	2ᵇ		—	—	1ᵃ	—	
				3	—	—	—	—		—	—	—	—	
14 Days	Whole Evap. Milk	5.90	*Line 3* Colonies present in pour plates made of primary culture after 2–5 days incubation. (Pour plates were incubated aerobically at 37°C.)	1	—	—	—	—		—	—	—	—	
				2	—	—	—	—		3ᵉ	—	—	—	
				3	—	—	—	—		—	—	—	—	
	Whole Evap. Milk	5.90		1	—	—	—	—		—	—	—	—	
				2	1ᵉ	—	—	—		—	—	—	—	
				3	—	—	—	—		—	—	—	—	
19 Days	Dil. Evap. Milk	7.00		1	—	—	—	—		—	—	—	—	
				2	—	—	—	—		—	1ᵃ	—	—	
				3	—	—	—	—		—	—	—	3ᶜ	
	Dil. Evap. Milk	7.00		1	—	—	—	—		—	—	—	—	
				2	—	—	—	—		—	—	—	—	
				3	—	—	—	—		—	—	—	—	
	Rabbit Blood Neopep. Broth	7.20		1	—	—	—	—		—	—	—	—	
				2	—	—	—	—		—	—	—	—	
				3	—	—	—	—		—	—	—	—	

* See * of Table 1 for explanation of symbols.
† Sterile distilled water was used. Solutions and media were sterilized by autoclaving.
a Subsurface and opaque, yellow surface colonies (Gram +cocci). Probably contaminants.
b Subsurface and opaque, white surface colonies (Gram −rods). Probably contaminants.
c Subsurface and opaque, white surface colonies (Gram +cocci). Probably contaminants.
d Subsurface and opaque, yellow surface colonies (Gram +cocci).

TABLE 3

Fluorescein (2 percent) in 1:5,000 solution of Zephiran chloride was contaminated by molds when cultured at the end of 7 days, but was sterile at the 14- and 19-day periods.

TABLE 4

Pilocarpine (1 percent) in 1:5,000 Zephiran chloride remained sterile during the 19 days of the experiment.

TABLE 5

Pontocaine (0.5 percent) in 1:5,000 Zephiran chloride remained sterile during the 19 days of exposure.

When 1 or 2 colonies were present in the pour plate, it was considered to be due to contamination at the time of subculturing, rather than that the organism was present in the primary culture.

Under the conditions of the experiment,

the control solutions of the drugs in sterile water all became contaminated, while the drugs in the 1:5,000 Zephiran-chloride solution remained sterile with the exception of the fluorescein which became contaminated by molds at the 7-day period, but which became sterile at the 14- and 19-day samplings.

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DISCUSSION

DR. M. H. POST, JR. (St. Louis Missouri): I had the privilege of some correspondence with Dr. Hughson concerning the injection of Zephiran chloride into the anterior chamber of the rabbit eye. The subject has been of interest to me, inasmuch as I have been recommending the use of Zephiran chloride in conjunction with other sterilizing solutions for the prevention of infection in cataract surgery.

A few experiments were carried out. In these it was found that: Using a solution of Zephiran chloride varying in strength from 1:3,000 to 1:500 the corneas of the injected eyes became diffusely cloudy in 5 or 6 days.

They remained so for about 5 weeks, clearing up at the end of that time. The irides on the other hand began to show signs of localized atrophy near the site of injection. This change was first manifest about 2 weeks after the injection, gradually becoming more marked as long as the animal survived.

Just a word, however, in conjunction with its effects on cataract surgery seems in order. It is of interest that, through a miscalculation a solution of Zephiran chloride, 1:500 was used in the operating rooms of the McMillan Hospital for a period of 30 days, and that during that time there were no complaints of corneal or iris disturbances. It would appear, therefore, that the small amount of Zephiran introduced into an open eye even though much stronger than necessary cannot be likely to produce any great damage.

Relative to maintenance of sterility in solutions, I am tremendously interested in what Dr. Hughson has had to say. I have found that the sterile water exposed to air for a few minutes in the trays in our operating rooms would result in 100-percent con-

tamination of the instruments after they had
been supposedly completely sterilized by the
other solutions.

By replacing the sterile water in these
trays by Zephiran solution, (1:3,000) this
difficulty was completely overcome, since the
Zephiran solution, thus substituted, re-
mained sterile for a period of 5 hours, that
is, as long as the experiments upon it were
conducted.

DR. ALSON BRALEY (New York, New
York) : I would like to ask a question. What
effect does Zephiran chloride have on the
presence of viruses in the solution?

DR. DAVID G. COGAN (Boston, Massachu-
setts) : I would like to ask the essayist if he
has had any experience with allergy to this
drug.

DR. PHILLIPS THYGESON (San Jose, Cali-
fornria) : I might say that the problem of
sterility of solutions is quite an important
one now that epidemic keratoconjunctivitis
is so widespread. The question as to whether
or not Zephiran is protective against this
virus is still open.

DR. HUGHSON (closing) : When I first
started to use Zephiran to replace the aque-
ous in the animal eye, it was to find out its
effect, as I was curious to find out what
would happen if any of the solution adhered
to a knife or keratome and to see how strong
a solution the eye could tolerate.

I think that with one drop of the Zephiran
adhering to the instrument and diluted by the
total aqueous, provided a solution of 1:3,000
or 1:5,000 is used, you have a safe antiseptic
agent.

The answer to Dr. Braley's question con-
cerning viruses. There has been no work
done on that as far as I could find in the
literature; the only thing that I can find that
might have some bearing on this is: I think
some authorities have an idea that possibly
bacteriophage may be allied to a virus. At
least, they resemble each other morphologi-
cally under the electron microscope and
Maier did some work with that on vaccines
and bacteriophage to preserve the sterility
of the solution; and as far as he could see,
Zephiran did not have any ill effect on the
quality of the bacteriophage, so I would
possibly deduce from that, that it would not
have any effect on the virus. I realize that
is a long stretch, but to my knowledge no
work has been done directly against the
virus.

As to the question concerning allergy, I
haven't found anyone who is particularly
sensitive. Occasionally, you will get a slight
hyperemia of the eye from the solution both
in human beings and in animals, but the tox-
icity of it or the lack of toxicity is pretty well
proven. Domagk, the original worker, used
Zephiran undiluted as the sole source of fluid
for animals for several months and could
find no damage of any sort. You do get,
occasionally, a case of slight hyperemia in
some people from it.

EFFECTIVENESS OF STREPTOMYCIN IN TREATMENT OF EXPERIMENTAL CONJUNCTIVITIS CAUSED BY *HEMOPHILUS SP.**

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AND

Margaret Pittman,[‡] Ph.D.

Bethesda, Maryland

Epidemic conjunctivitis, commonly called "gnat sore eyes," has been described in certain sections of southern United States.[1,2] In a bacteriologic study of 50 cases in Georgia, in 1932, Bengtson[2] isolated organisms resembling the Koch-Weeks bacillus from 80 percent of the cases. While the disease is usually mild, is of short duration, and leaves no sequelae, severe and prolonged cases do occur, and the high incidence especially in school children renders it one of major public health importance in certain areas.

During October, 1947, a study of the disease in the Rio Grande River Valley, where it has been prevalent for many years, was initiated at the request of the Hidalgo-Starr Counties Medical Society and the National Society for the Prevention of Blindness. This investigation was directed toward the elucidation of the etiology and epidemiology of the disease as it occurred in that region.

During the course of this investigation scrapings and cultures were taken from the conjunctivas of 45 acute cases and examined for pathogenic organisms. From 24 of these cases a small, gram-negative bacillus resembling Hemophilus influenzae was isolated. All strains failed to grow on plain nutrient agar. Twelve were lost before the growth factor requirements could be determined. The remaining 12, however, required both X and V factors, and reduced nitrates to nitrites. Eleven appeared to be non-type-specific, the other was type b. Only

the latter produced indol. Because of the lack of any criteria for differentiation, the Koch-Weeks bacillus and the influenza bacillus have been considered as belonging to the same species.[2,3] However, until further study has been made, we prefer not to designate the strains recovered from the eye in this study as Hemophilus influenzae. For convenience they will be referred to as Hemophilus sp.

Hewitt and Pittman[4] reported the sensitivity of H. influenzae to streptomycin in vitro. With their technique the Texas eye strains were found to be inhibited by 0.625 or 1.25 micrograms (units) of streptomycin per ml., which falls within the range of sensitivity of H. influenzae. Rivanol lactate (2-ethoxy-6, 9-diaminoacridine lactate) was bactericidal in concentrations of 12.5 to 25 micrograms per ml.

Despite the frequent occurrence of this organism in the conjunctivas of acute cases, the question remained whether this agent by itself could cause a conjunctivitis in human beings or was merely incidental or accessory to an undetected cause. Attempts to induce infection in the eyes of rabbits and monkeys with cultures of these strains alone, mixed with cultures of Staphylococcus albus, or subsequent to scarification failed.

EXPERIMENTAL STUDY

SUBJECTS

However, an opportunity was afforded to inoculate 8 human volunteers with a strain of Hemophilus sp. The volunteers were healthy young adult white men, aged 19 to 39 years, who had had experimentally induced common colds 10 days previously, but had become almost entirely free of symptoms.[5]

They were kept together in a ward, iso-

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lated by strict techniques, and observed constantly by a male nurse and trained attendants. Temperatures were recorded at least every four hours during the daytime. Urinalysis and leukocyte counts were done daily and differential leukocyte determinations made every other day.

Bacteriologic cultures of each eye were taken before inoculation and each day during the course of the infection. Cotton swabs moistened with broth were rubbed gently along the lower conjunctival sac, incubated in 0.15-percent agar infusion broth containing approximately 3-percent Fildes peptic digest of blood to supply the X and V growth factors for 3 to 4 hours, and then streaked on blood agar and nutrient agar also containing peptic digest of blood.

STRAIN USED FOR INOCULATION

The strain used for inoculation, No. 48, had been isolated from the conjunctiva of a 7-year-old Hidalgo County school girl who had a mild conjunctivitis of 30 hours' duration. It had been preserved in the dried state soon after the original isolation. A 5-hour broth culture was diluted with normal saline solution so that the inoculum of 0.1 ml. contained not more than 10,000,000 bacteria. This was instilled directly into the right eye of each volunteer about 3 P.M. on the first day of the study.

RESULTS

Six of the 8 inoculated volunteers developed a severe conjunctivitis corresponding clinically to that observed among the population of the Rio Grande River Valley, and a hemophilic bacterium indistinguishable from the inoculated one was recovered from the affected eyes. The other 2 volunteers showed evidence of slight conjunctival hyperemia only on the first day after inoculation.

The signs and symptoms in all 6 cases were uniform, although there was variation in the degree of intensity in individual cases. Despite the recent convalescence from the common cold, respiratory symptoms were minimal throughout the course of the infection. A representation of the degree of intensity of the clinical findings including conjunctival injection, mucopurulent discharge, edema, pain, and photophobia is presented in the chart along with the record of the isolation of Hemophilus sp. and the type of therapy employed.

In general the first symptom noticed by the patients was an itching or scratching of the inoculated eye about 6 hours after instillation of the culture. The following morning the eyelids were adherent with dried exudate, the eye was painful, the bulbar and palpebral conjunctivas were hyperemic, and a moderate amount of yellow mucopurulent material was present in the conjunctival sac. In some there was definite bipalpebral edema.

On the third day, 48 hours after inoculation, all the signs and symptoms were exaggerated and the bipalpebral edema was increased to the extent of closing the eye in some cases. Photophobia was more pronounced. In general there was slight elevation of temperature, not exceeding 1-degree Fahrenheit, and no marked change in leukocyte count or urinalysis.

In 2 cases (Cases 1 and 2), not specifically treated till the 8th and 9th day, the disease progressed to a severe, acute manifestation of all the local signs and symptoms, as well as definite general malaise. In three instances (Cases 2, 6, and 8,), the left or uninoculated eye became infected spontaneously as shown by the clinical appearance and the presence of Hemophilus sp. in culture.

On the third day, or 48 hours after inoculation, the 8 patients were separated into 3 groups for evaluating specific treatment. Streptomycin hydrochloride* in a concentration of 1 mg. per ml. of 0.85 percent NaCl solution was applied locally with an eyecup to the affected eye of three patients (Cases 3, 5, and 6) every 2 hours from 6 A.M.

* Furnished by the Division of Research Grants and Fellowships, National Institute of Health.

Chart 1 (Davis and Pittman). Clinical evaluation, isolation of Hemophilus sp., and type of therapy in eight human cases of experimental conjunctivitis.

until 10 P.M. for various time periods as indicated in the chart.

A second group (Cases 4, 7, and 8) was treated similarly with a mixed solution of streptomycin in the same concentration, and rivanol lactate in a concentration of 0.2 mg. per ml.

Patients in Cases 1 and 2 were treated locally with 0.85-percent NaCl solution till the 8th and 9th day as a control for the specific therapy administered to the other cases. Patients in Cases 3 and 4 showed only slight evidence of infection on the 2nd day and were treated as a check on the possible

irritative effect of the two specific solutions.

The four cases (Cases 5, 6, 7, and 8) manifesting acute disease and treated early with specific therapy showed marked clinical improvement beginning about 8 or 10 hours after the start of treatment, with definite relief of pain and diminution of the exudate. The following day there was less conjunctival hyperemia and Hemophilus sp. could no longer be recovered from the treated eye. Convalescence was rapid and progressive, and the eye cultures remained negative.

Since there was such a uniformity of clinical findings and the experimental conditions of the disease were relatively constant, only two case histories are presented. Case 1 on the 3rd day appeared to have a representative case and, as a control, specific therapy was withheld till the 8th day. Case 6 was more severe, and streptomycin eye washes were administered 48 hours after inoculation and continued for 3 days.

CASE REPORTS

Case 1. This 39-year-old volunteer first noticed itching, burning, exudate, and conjunctival injection of the right eye upon awakening in the morning, 15 hours after inoculation. The signs and symptoms became more severe and on the 3rd day, 48 hours later, there was moderate bipalpebral edema as well.

As a control for those patients receiving specific therapy, the affected eye was treated with 0.85-percent NaCl solution as an eye wash in an eyecup for the affected eye every 2 hours from 6 A.M. until 10 P.M.

The severity of the disease increased till the 8th day when there was marked bipalpebral edema, pain, severe hyperemia, and injection of the bulbar and palpebral conjunctivas, and profuse mucopurulent exudate. At this time he complained of a dry nonproductive cough.

The temperature reached 99°F. on the 6th day and 99.2°F. on the 8th day. Leukocyte counts varied from 7,600 to 12,000 cells

per cubic mm. and the urinalysis was normal. On the 8th day streptomycin therapy was instituted. The following morning the patient reported marked lessening of pain, discomfort, and exudate, and the conjunctival injection was less intense. Improvement was steady till the 13th day when therapy was discontinued, and the only sign remaining was a slight hyperemia of the right conjunctivas.

Bacteriologic culture taken just before inoculation revealed the presence in the right eye of a non-type-specific strain of Hemophilus influenzae which produce indol. Cultures made daily from each eye showed a heavy growth, from the 2nd until the 8th day, of a strain of Hemphilus which was indistinguishable from No. 48, the inoculated strain. At no time was an organism isolated which resembled H. influenzae, the one originally found in the right eye. No hemophilic organisms were recovered from the eye subsequent to the institution of streptomycin solution eye washes.

Case 6. This 22-year-old volunteer reported itching at the right eye about 6 hours after inoculation, and on the following day there was marked conjunctival injection, pain, and a moderate amount of mucopurulent discharge from the right eye. On the 3rd day the disease had progressed, palpebral edema was marked, and the right nostril was obstructed and draining a watery discharge.

At this time local application every 2 hours of streptomycin solution (1 mg. per ml.) employing an eyecup was started. About 8 hours after the start of specific therapy, the patient reported a lessening of discomfort.

On the 4th day there was much less exudate and edema and somewhat less conjunctival hyperemia. However, the left eye was acutely inflamed, edematous, painful, and discharged mucopurulent material. Streptomycin eye washes were instituted for this eye at this time.

On the 5th day there was marked improvement in both eyes, and on the 6th day

only a mild conjunctival hyperemia remained in either eye after 72 hours of treatment for the right eye and 48 hours for the left eye. Therapy was discontinued and no recurrence of symptoms was noted during the following week of close observation.

There was a slight elevation of temperature not exceeding 1-degree Fahrenheit from the 2nd to the 6th day and occasionally thereafter, possibly due to a subcutaneous inflammation on the left cheek of unknown cause. The highest leukocyte count was 7,700 cells per cubic mm. and the daily urinalysis was normal.

Bacteriologic culture from the eyes taken before inoculation of the infecting organism revealed no known pathogen. Hemophilus sp. was recovered from the right eye in heavy growth on the 2nd and 3rd day and from the left eye on the 4th day. It was not recovered from either eye after specific therapy was started.

DISCUSSION

The immediate effectiveness of streptomycin and streptomycin in combination with rivanol lactate applied locally to the infected eye in relieving the signs and symptoms and reversing the cultural findings is encouraging. It remains to be determined whether other methods of topical application—that is, by instillation or irrigation—and a less rigid treatment schedule would be as effective.

It should be emphasized that the infection treated in this series was localized in the eye and not the respiratory tract, and that intensive treatment was directed against the primary focus. It is possible that cases of conjunctivitis due to Hemophilus influenzae which may be secondary to or concurrent with a primary infection of the respiratory tract would not respond to topical therapy in the same way.

SUMMARY

Acute conjunctivitis resembling clinically that seen in the Rio Grande River Valley was induced in 6 of 8 human volunteers with a culture of Hemophilus sp. isolated from a Texas case, and an organism indistinguishable from the one inoculated was recovered from the affected eyes.

Two acute infections were treated with a solution of streptomycin hydrochloride, (1 mg. per ml.) applied locally in an eyecup, and 2 cases were similarly treated with a combination of streptomycin and rivanol in solution.

The clinical condition improved rapidly, and Hemophilus sp was not isolated from the eyes after the institution of treatment. In 2 cases treated with 0.85-percent NaCl solution as an eye wash, the disease progressed and Hemophilus sp. persisted until the 8th and 9th day when the institution of streptomycin therapy was followed by rapid clinical improvement, and failure to recover the organisms.

National Institute of Health.

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DISCUSSION

DR. KENNTH C. SWAN (Portland, Oregon): In January, 1947, I reported to the Research Study Club of Los Angeles an epidemic of acute conjunctivitis. With some 30 cases, it was possible to treat one eye with streptomycin ointment and the other eye with the ointment base alone. I have forgotten the concentration of streptomycin in the ointment. In that particular oubreak which occurred in Portland, Oregon, the organism was Hemophilus influenzae, although the type was not determined. The results in the streptomycin-treated eye were quite spectacular. In many of the patients, symptoms in the treated eye subsided rapidly after two applications several hours apart. This led several patients to discontinue the ointment in the treated eye and to apply it to the control eye, and then to discontinue treatment. Two of these patients had recurrences. In treatment of the recurrences, the streptomycin ointment was not nearly so effective. We interpreted this decreased response as illustrative of the fact that organisms rapidly became fast to the streptomycin, if treatment is inadequate. I would like to hear the essayist comment on this matter.

Another outbreak of Hemophilus influenzae conjunctivitis occurred last spring in the Portland area but the infection was so mild and of such short duration that it was not always possible to tell the difference between the treated and the untreated eye. The conjunctivitis would clear up in 36 hours; therefore, I did not feel justified to use streptomycin in the hundred or so mild cases of this second outbreak.

DR. JAMES H. ALLEN, (Iowa City, Iowa): In the Midwest we do not find the Koch-Weeks organism, but we do see many cases of conjunctivitis caused by H. influenzae or H. hemolyticus. It is our impression that these infections usually respond readily to treatment with any of the usual conjunctival antiseptics. The lesion most frequently seen is acute catarrhal conjunctivitis with an occasional severe purulent conjunctivitis.

However, I do recall one severe and prolonged unilateral case of conjunctivitis due to H. influenzae. It finally responded to the instillation of drops of streptomycin (100 mg. per cc.). Therefore I would like to ask Dr. Davis if any of his cases tended to remain unilateral? And if he has an explanation for the apparent unusual resistance of these strains of hemophilus to chemotherapy?

DR. ALSON E. BRALEY (New York City): I was very much interested in the disease down there in Texas, this "gnat" conjunctivitis. I saw several of the slides and from the description obtained from the patients with the disease some time ago, there were many particles or whatever you might call them in the slides that could be a very small Hemophilus influenzae. I thought they might possibly be Rickettsia. In the next paper, I think we will have something much more valuable than streptomycin.

DR. PHILLIPS THYGESON (San Jose, California): I should like to make a few comments. When I first became interested in the bacteriology of the eye, while at the University of Iowa, I tried to find a typical Koch-Weeks organism. We had many cases of rather mild, subacute conjunctivitis, such as Dr. Allen has described, but there was only one case that turned out to be typical Koch-Weeks conjunctivitis; this was in a student who was on a motor trip from California.

It seemed to me that there was a clinical distinction, in any event, between the subacute conjunctivitis, from which morphologically typical influenza bacilli could be demonstrated, and the acute conjunctivitis containing typical Koch-Weeks bacilli. In the former the bacilli were characteristically coccobacilli and there was usually an excess of mucus over polys, while in the latter, or typical Koch-Weeks conjunctivitis, the bacilli were slender rods and the exudate was

frankly purulent with a minimum amount of mucus. Thus there appeared to be two types of conjunctivitis associated with hemophilus organisms.

It is true that by ordinary culture methods there were no differences between the hemophilus organisms from these two types of cases, but no typing was done and I have seen no reports as yet of the typing of hemophilus organisms from conjunctivitis. I should therefore like to ask the essayist if he thinks it is possible to settle this question of the relationship or identity of the influenza and Koch-Weeks bacilli.

I should like to comment on the so-called "gnat" conjunctivitis that we have in the Imperial Valley of California. The Imperial Valley, particularly around Indio, is a very hot, dry area comparable, I think, to southern Texas, and there are the same types of recurrent periodic epidemics of acute conjunctivitis associated with gnats and apparently aggravated during the gnat-breeding season, and in which the typical Koch-Weeks organism has been found.

The cases of this condition that I have seen have all been of the acute, severe type and none have been of this milder type observed in Iowa and described by Dr. Allen. I am wondering if the essayist can make any comments on the possible relationship of this California gnat conjunctivitis to the south Texas type.

DR. DAVID G. COGAN (Boston, Massachusetts) : I believe I am correct in saying that in Boston conjunctivitis from Hemophilus influenzae is practically nonexistent in adults. We do have an occasional infection in children, perhaps preferentially in girls, caused by this organism but the clinical picture is unlike that described by the authors in being bilateral and having more evidence of keratitis (lacrimation, photophobia, punctate fluorescein staining) along with the conjunctivitis. I should like to ask the essayist or Dr. Thygeson if they are familiar with such a clinical picture occurring predomi-

nantly or exclusively in children.

DR. DAVIS (closing) : First, in regard to this problem of the fastness or resistance of a hemophilus organism to streptomycin, we were well aware of that and made some laboratory experiments to try to shed some light on it. We carried this strain and several strains for about 15 passages through increasing amounts of streptomycin and we were able to increase its resistance about 80 times to streptomycin.

At the same time, Dr. Pittman felt that perhaps if we added another antibacterial agent to the streptomycin, we might be able to reduce that tendency to develop resistance. We selected rivanol. She found in some preliminary experiments that the organisms apparently did not develop resistance to streptomycin as readily in solution of rivanol as when it was in streptomycin alone, and that was the reason we used the streptomycin and rivanol, particularly in these patients.

In regard to the disease in Texas, it is a very severe disease ; my experience with conjunctivitis in the rest of the country is extremely limited, but it does not correspond with the ordinary conjunctivitis which has been described, and as Dr. Thygeson said, it does seem to be somewhat different.

As far as the other causes of the disease, we did everything we could with material from these cases to find out some other cause. We searched the stained slides for evidence of Rickettsial bodies or the elementary bodies of trachoma or inclusion conjunctivitis and were able to identify only one case of trachoma among a large number of cases.

We inoculated a great many animals with material that was brought back in a frozen state to the laboratory but we were able to secure no evidence at all of any other cause of the disease.

In regard to this problem of Koch-Weeks, I am sorry that Dr. Pittman isn't here because she could discuss it much more capably than I. As you know, Koch reported seeing the organism in Egypt and Dr. Weeks was

able to culture it, but only in association with another organism, in New York in 1886 and 1887.

This organism which we dealt with down there could be the same as Koch and Weeks wrote about; however, taxonomically, the Koch-Weeks bacillus is not a recognized species, and there are no type strains; none of the organisms which were originally described of course are in existence now.

The organisms which were subsequently isolated from the eye have been indistinguishable from Pfeiffer's influenza bacillus according to our present methods of bacteriologic technique, and they have been considered the same organism in Bergey's *Manual of Determinative Bacteriology*. However, with more recent advances in technique, particularly in the knowledge of the nutritional requirements of this very interesting group of Hemophilic organisms, we may be able to determine whether these strains recovered from the eye are the same

as those recovered from respiratory infections.

As far as this disease compares with other conjunctivitis, particularly among children in other parts of the country, I cannot discuss that adequately because of my limited experience with the disease in other parts of the country. However, it is a very severe disease, as you can see, in the southern United States. It is a disease chiefly of children and occurs mainly in the group under five years of age; it is a disease of people of poor and economically low status, although it spares no one.

It is both highly contagious and infectious. Whole families will be infected and one after the other will come down with it. It may last for a short period of time only with a very mild case, and many are self-limited; or it may persist for several weeks, up to six weeks or longer. Some of the patients we saw were said to have had it for six weeks or two months.

AUREOMYCIN IN OCULAR INFECTIONS*

A STUDY OF ITS SPECTRUM

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Aureomycin is an antibiotic obtained from a mold belonging to the Streptomyces group. It was isolated by workers at the Lederle Laboratories of the American Cyanamid Company.[1] This antibiotic was found by these workers to be effective against both Gram-positive and Gram-negative organisms, and their work suggested a wide range of activity. It has been made available to us in two forms, Aureomycin hydrochloride and Aureomycin borate.

Aureomycin HCl is a dry, crude, crystalline substance, yellow in color. When in aqueous solution it is an acid with a pH of 3.0 and is stable either in the dry form or in solution without refrigeration. In solution it can be injected intramuscularly. The dry material is quite soluble in water or normal saline; 20 mg. will dissolve in 1 cc. to 1.5 cc. of normal saline. This material is moderately irritating when injected intramuscularly, but with the addition of a small amount of procaine hydrochloride there is little or no discomfort.

A borated salt of Aureomycin was also manufactured and dried into a fine, yellow, stable powder. In aqueous or physiologic saline solution the pH is 7.5 to 7.8. It is very soluble in nearly all concentrations; however, in solution at room temperature the material loses its antibiotic activity within approximately 24 hours. Various concentrations of the borate were used, but it was found that a 0.5-percent solution was the one best tolerated. The activity of the 0.5-percent solution is retained for several days when it is stored at +4°C. Freshly prepared Aureomycin-borate solution is a light golden-yellow color;

after it has remained at room temperature for 24 hours, it turns a golden-brown.

Wong and Cox[2] have shown in experimental infections with a wide range of microörganisms, rickettsia, and viruses that Aureomycin was unusually potent and active. Since this was true experimentally, it was felt that this new antibiotic should be tried in many types of ocular infections. The antibiotic was used in this study much the same as penicillin might be used clinically. The borated salt was used locally in eyes for infections of the conjunctiva and cornea. When infection was present in the deeper structures of the eye, such as uveitis and in ocular infections associated with general disease, the local application was augmented by intramuscular injections of Aureomycin HCl.

In a previous report 100 patients with conjunctival and corneal infections have been reported.[3] It was found from this study that local use of Aureomycin borate effectively inhibited staphylococci, pneumococci, and H. influenzae. It was also active against the virus of inclusion conjunctivitis and appeared to have some value in herpes simplex corneae and to a lesser extent in epidemic keratoconjunctivitis. Since that time additional information has been obtained regarding these same organisms, as well as other ocular infections.

The present study was made in an attempt to find the number of diseases and microorganisms in which Aureomycin might be effective. The use of Aureomycin in 401 unselected cases showed that the antibiotic was effective in the treatment of 303 and of no value in 98. This can be further separated into 383 cases in which the infection was primarily of the conjunctiva and cornea and

18 cases in which the infection was primarily of the uvea.

STAPHYLOCOCCAL INFECTIONS

In all, 202 patients with various types of staphylococcal infections were treated. The majority had blepharitis combined with a conjunctivitis, and keratitis. There were, however, a fair number of cases with marginal infiltrates and marginal ulcers associated with the chronic conjunctivitis. A few patients had hordeola and chalazia complicating the blepharitis.

For statistical purposes we divided staphylococcal infections into mild and severe cases. There were 47 patients in the group considered mild, those with a blepharitis squamosa and a chronic conjunctivitis associated with a slight discharge. Severe staphylococcal infections were those with a blepharitis with an acute or subacute conjunctivitis combined with corneal changes such as superficial punctate keratitis, marginal infiltrates, or marginal ulcers.

The evaluation of the results of Aureomycin in staphylococcal infections was difficult because of the tendency for recurrence of all types of staphylococcal infections, and the inclination of the patient to discontinue treatment as soon as the acute symptoms subsided. In order to evaluate the effectiveness of the antibotic an arbitrary 48 hours was chosen as the time limit for disappearance of symptoms; if there was no improvement in the objective appearance or symptoms, the action of the antibiotic was considered unfavorable.

There is little doubt, as reported in the previous publication, that Aureomycin is very active against the staphylococcus, whether the disease produced by it is mild or severe. From experience with these patients it seems to be as potent as local penicillin (1,000 units per cc).

Staphylococcal conjunctivitis had a tendency to recur when therapy was discontinued; recurrences were about the same with Aureomycin as with other local anti-

biotics. Aureomycin was potent in patients with staphylococcal conjunctivitis who had developed a sensitivity to the local use of penicillin.

Staphylococcal infections require local therapy for a long period of time and since a transition occurs in Aureomycin borate solution, an attempt was made to prepare an ointment with both the hydrochloride and the borate. The hydrochloride ointment was irritating to nearly all of the patients although it seemed to be active against the infection. The ointment prepared with the borate was nonirritating but it probably lost its activity after a short period. Further investigation will be necessary to determine the best means of retaining this antibiotic effect for the required prolonged use in staphylococcal infections.

There were 12 unfavorable responses to Aureomycin in the entire group. The organisms could have been assayed to determine the amount of the antibiotic necessary to inactivate them, but it is possible that the patients did not use the antibiotic as directed.

PNEUMOCOCCAL CONJUNCTIVITIS

The second largest group of patients with bacterial conjunctivitis was infected by the pneumococcus. The patients with pneumococcal conjunctivitis have been treated; there were excellent results and no recurrences.

MENINGOCOCCAL CONJUNCTIVITIS

In one case the response to local Aureomycin was prompt.

INFLUENZAL CONJUNCTIVITIS

The response of 8 patients from whom influenza bacilli were cultured from the conjunctiva was rapid and efficient. In all of the patients the purulent discharge was entirely gone within 24 hours. It was difficult to evaluate the antibody response to influenzal conjunctivitis since the duration of this infection without treatment varied considerably. From the appearance of the conjunctiva, however, we felt that Aureomycin

was potent against H. influenza. **Further investigation** will be necessary, particularly in influenzal meningitis, to determine the degree of potency.

DIPLOBACILLARY INFECTIONS

The diplobacillus of Morax-Axenfeld has been an organism which has not responded well to any form of therapy. In 5 cases the symptoms were relieved and no bacteria found on scrapings of the conjunctiva after local use of Aureomycin. In one patient a recurrence developed in one eye shortly after the antibiotic was discontinued, while in 3 patients no definite improvement was noted. From all clinical appearances, however, Aureomycin is much more effective against the diplobacillus than any other therapy.

E. COLI

Aureomycin borate was used in only one case of infection of the conjunctiva by E. coli. A pure culture of E. coli was obtained from the conjunctiva after several months of conjunctivitis. Following the use of this antibiotic for 24 hours, conjunctival symptoms were entirely gone and the conjunctiva was free of organisms.

PROTEUS VULGARIS INFECTIONS

Of 3 cases, one showed improvement following Aureomycin therapy. There was one recurrence which responded to a second course of treatment. The third case showed no improvement.

VIRAL INFECTIONS

Two viruses involving the conjunctiva and cornea have been treated with Aureomycin, 21 cases of dendritic keratitis and 53 cases of epidemic keratoconjunctivitis. Clinically Aureomycin appears to be more useful in the herpes corneae virus than in epidemic keratoconjunctivitis.

DENDRITIC KERATITIS

All 21 of the patients with dendritic keratitis had an associated beginning involvement of the corneal stroma with an area of infiltration under the dendritic figure. In 13 of these patients the results after use of Aureomycin were rapid and beneficial. The ulcer was healed in 24 hours and there was no increase in the size of the infiltrate beneath the ulcer, and in most of the patients the infiltrate disappeared entirely. In one patient who had a recurrent dendritic keratitis with a large disciform keratitis there was no appreciable change in the involvement of the corneal stroma after Aureomycin. Seven patients showed no improvement. From our experience thus far with the antibiotic, it seems to be a valuable therapeutic agent for dendritic keratitis.

EPIDEMIC KERATOCONJUNCTIVITIS

The use of Aureomycin in the treatment of epidemic keratoconjunctivitis does not appear effective from the data presented. Fifty-three patients with the infection have been followed after the use of the antibiotic. There were many more patients with epidemic keratoconjunctivitis who had used Aureomycin, but their follow-up was not entirely satisfactory and they cannot be included in the series.

The course of the disease was not affected in 28 of the 53 patients, but 25 showed a definitely favorable reaction. These patients taught us a good deal as to how this new antibiotic should be used. Certainly in epidemic keratoconjunctivitis, Aureomycin must be used before corneal opacities begin, since in several of the 28 patients it was started after corneal opacities were first noted.

It appears that if Aureomycin can be started before the 3rd to 5th day of the disease and used continually for at least a week or 10 days there is some beneficial effect. If the material is instilled in the conjunctival sac every one-half to one hour and continued, even though the symptoms and edema of the conjunctiva increase, there will certainly be some favorable result.

Most of the 25 favorable cases developed 1

or 2 typical corneal opacities at about the same time as they would had the disease been allowed to run its normal course, but the conjunctival findings and the corneal changes were considerably decreased as compared to control cases. Even though Aureomycin was used, a few developed conjunctival scars and minimal symblepharon.

Patients who used the antibiotic a few times and discontinued its use after 24 or 48 hours because of its slight irritability received no benefit from the antibiotic. The method of choice, therefore, in treatment of epidemic keratoconjunctivitis should be the instillation of Aureomycin borate every hour for at least 10 days with a fresh supply of the antibiotic given at 48-hour intervals. Blood has been obtained from the patients for neutralization of the virus to determine the presence of antibodies.

FOLLICULAR CONJUNCTIVITIS, UNKNOWN ETIOLOGY

The evaluation of the use of Aureomycin in follicular conjunctivitis is rather difficult since this group contains a number of patients with what clinically appeared to be a Beal's type of conjunctivitis. This type of follicular conjunctivitis is notoriously inconsistent in the duration of symptoms. With Aureomycin, however, none of the cases of follicular conjunctivitis lasted more than 48 hours.

INCLUSION CONJUNCTIVITIS AND TRACHOMA

Local Aureomycin was used in 6 cases of inclusion conjunctivitis. Most of these were in the newborn infant after the disease had been present for from 5 days to 2 weeks. The response to Aureomycin was prompt and the purulent discharge was entirely gone after 24 hours of its use. The conjunctiva returned to normal within 3 days to 1 week. Some of the cases have been followed with daily scrapings from the conjunctiva ; no inclusion bodies could be found after 24 hours on Aureomycin.

One case of trachoma III which had been recurrent for 20 years was treated. This patient had developed anuria on sulfanilamide. Following treatment with local Aureomycin there was rapid disappearance of corneal infiltrates and conjunctival symptoms. No inclusion bodies could be demonstrated from the conjunctival scrapings. From the effect of Aureomycin on inclusion conjunctivitis and lymphogranuloma we feel that it should also be effective in trachoma.

MOLLUSCUM CONTAGIOSUM

One patient with molluscum contagiosum has been treated with Aureomycin locally. There was no effect on the tumor or on the appearance of the conjunctiva.

KERATITIS

Of the various types of keratitis, 34 cases have been treated. Some of these have been remarkable, particularly one patient with a severe marginal keratitis of unknown etiology. This patient had marked thinning of the periphery of the cornea, and the central cornea was necrotic. His vision was reduced to hand movements in one eye and 20/400 in the other eye. After local and parenteral Aureomycin the process stopped and the central portion of the cornea became clear while the periphery vascularized. The vision was restored to 20/25 in one eye and 20/20 in the other.

Six cases of acne rosacea keratitis have been treated, 1 with some beneficial effect and 5 without any effect. It is doubtful that any of the various types of keratitis profunda or severe types of keratitis are particularly benefited by Aureomycin although 9 of the 16 cases improved under Aureomycin therapy.

Pyocyaneus infections of the cornea were not helped by treatment.

Two patients with neurotropic type of keratitis were unaffected by Aureomycin.

PARINAUD'S CONJUNCTIVITIS

Only 2 patients with Parinaud's conjunctivitis were treated with Aureomycin with no

effect on the progress of the disease in one case and slight improvement in the other.

VERNAL CONJUNCTIVITIS

Of the 8 cases of vernal conjunctivitis which have been treated with varying amounts of local Aureomycin, 6 were unchanged but 2 showed a disappearance of the filmy membrane and some relief of symptoms, although there was no changt in the papillary hypertrophy in the conjunctiva. It is probable that the improvement was due to the antibiotic action on the secondary infection.

UVEITIS

All of the patients with uveitis have been treated with local borate salt and intramuscular Aureomycin HCl. Of the 18 patients with various types of uveitis, 8 have shown beneficial results while 10 have remained unchanged.

The most striking in this group are 2 patients with scrofuloderm combined with keratitis and uveitis. Not only was the eye restored to normal vision, but there was also marked improvement in the draining sinuses and skin reaction associated with the underlying lymph-node disease. In one of these patients tubercle bacilli were demonstrated in biopsies of the lymph nodes, and in the other the biopsy and guinea-pig inoculation were unsatisfactory.

There are under observation at the present time two other patients with tuberculous lymphadenopathy and keratitis. The response of the cornea has been prompt, but there has been no change in the lymphadenopathy so that these cases have not been included in this study. The response to Aureomycin in these cases is certainly as satisfactory as with streptomycin.

One patient with a recurrent unilateral uveitis in whom a positive Frei test was found responded dramatically to treatment with Aureomycin. She developed a recurrence two weeks after receiving 100 mg. intramuscularly and was given another course of 100 mg. with complete recovery.

Seven cases of uveitis of unknown etiology have received Aureomycin; 4 have shown definite improvement while 3 have remained unchanged. Several more patients are under observation at the present time, but the effectiveness of the antibiotic is doubtful.

Two cases of sympathetic ophthalmia were given Aureomycin without any beneficial result, although one patient insisted on receiving it for a long period of time because he stated that his eyes felt better; there was no change in the clinical appearance of the eye.

One patient with a metastatic endophthalmitis of unknown etiology has been treated. She had developed a large abscess in the vitreous with pus in the anterior chamber following considerable abdominal surgery. She was given 300-mg. intramuscular Aureomycin and local drops after which all of the pus disappeared. A red reflex could be obtained from the fundus but, because of the vitreous opacities, it was impossible to see the fundus details at the time of her discharge from the hospital. The eye has remained quiet since that time.

COMMENTS

We have previously reported on the antibiotic properties of local Aureomycin in staphylococcal, pneumococcal, and influenzal conjunctivitis. To this group we are adding the diplobacillus of Morax-Axenfeld and E. coli. Several diseases of unknown etiology were treated in an attempt to determine the spectrum of the antibiotic.

The validity of Aureomycin in some of the virus infections was not anticipated. From the experiments of Wong and Cox[2] we learned that it should be of value in the psittacosis-lymphogranuloma group and in rickettsial diseases.

In our experience Aureomycin was excellent in the treatment of inclusion conjunctivitis. Because of the similarity between the virus of trachoma and the virus of inclusion, it should be a useful therapy for trachoma.

Aureomycin seems to have some antibiotic properties to the virus of herpes simplex. The results of its use on herpes infections of the cornea were striking. Experimental herpes-simplex infections will be reported later, although at the present time they indi- ate had been used for a period of 48 hours, it became somewhat irritating to the conjunctiva, in cases of epidemic keratoconjunctivitis particularly, and many patients thought it produced a more severe conjunctivitis. We found that the applications

TABLE 1

RESULTS OBTAINED IN AUREOMYCIN TREATMENT OF 401 OCULAR INFECTIONS

Infection	No. of Cases	Clinical Cure	No Improvement
Conjunctivitis			
Staphylococcus aureus			
mild	47	40	7
severe	155	150	5
D. pneumoniae	10	10	
Meningococcus	1	1	
H. influenzae	8	8	
Moraxella lacunata (diplobacillus of Morax-Axenfeld)	9	5	4
E. coli	1	1	
Proteus vulgaris	3	2*	1
Follicular (etiology unknown)	17	17	
Inclusion conjunctivitis	6	6	
Trachoma	1	1	
Vernal	8	2	6
Epidemic keratoconjunctivitis	53	25	28
Molluscum contagiosum	1		1
Parinaud's conjunctivitis (leptothricosis)	2		2†
Keratitis			
P. Pyocyaneus	2		2
Dendritic (herpes simplex)	21	13	8
Unclassified (etiology unknown, probably infectious)	16	9	7
Acne rosacea	6	1	5
Superficial punctate (virus?)	7	2	5
Neurotropic	2		2
Marginal, severe	3	2	1
Herpes zoster	2		2
Pinguecula	1		1
Episcleritis	1		1
Uveitis			
Idiopathic	7	4	3
Lymphogranuloma	1	1	
Scrofuloderm with uveitis and keratitis	2	2*	
Sympathetic ophthalmia	2		2
Endophthalmitis, metastatic	1	1	
Ritter's syndrome	1		1
Bechet's syndrome	2		2†
Harada's syndrome	2		2
Total	401	303	98

* One case recurred but responded to a second course of treatment.
† One case showed some improvement.

cate that Aureomycin has some antiviral properties.

Its use in epidemic keratoconjunctivitis is not entirely satisfactory, but there is a strong indication from several patients that if the antibiotic is used properly considerable benefit may be expected. After Aureomycin bor- of the antibiotic must be continued in spite of increased symptoms in order for it to be beneficial. There is no change in epidemic keratoconjunctivitis much short of a week. If the material was used conscientiously by the patient, the period of morbidity was shortened from approximately 3 weeks to a

TABLE 2

Ocular infections which should respond well to Aureomycin therapy

Virus infections
  inclusion conjunctivitis*
  trachoma*
  lymphogranuloma venereum†
  herpes simplex corneae*
  follicular conjunctivitis*
Hemolytic streptococcus infections
  conjunctivitis† (membranous)
  corneal ulcers†
  endophthalmitis†
  orbital cellulitis†
  impetigo*
Staphylococcus infections
  dacryocystitis
  conjunctivitis*
  ulcers*
  endophthalmitis†
  blepharitis*
  orbital cellulitis
  impetigo*
Pneumococcus infections
  dacryocystitis
  conjunctivitis*
  ulcers†

  endophthalmitis
  orbital cellulitis
Conococcus infections
  conjunctivitis
  iridocyclitis
Proteus infections
  conjunctivitis
Coliform group infections
  conjunctivitis*
H. influenzae infections
  conjunctivitis*
  ulcers†
  orbital cellulitis
Diplobacillus (Morax-Axenfeld)
  conjunctivitis*
  ulcers†
Friedländer bacillus infections
  ulcers†
  conjunctivitis*
  meibomitis†
  dacryocystitis
Meningococcus infections
  endophthalmitis
  conjunctivitis

* Local therapy preferred.
† Combined intramuscular and local therapy preferred.

TABLE 3

Ocular infections in which Aureomycin may be of value and deserves trial

Virus infections
  epidemic keratoconjunctivitis*
  herpes zoster†
  herpes simplex corneae*
Tuberculosis
  conjunctivitis* (ulcers)
  uveitis†
  keratitis
  scrofuloderm†
  kerato-uveitis
Nonhemolytic streptococcus infections
  orbital cellulitis
  endophthalmitis
  corneal ulcers

Brucella melitensis-abortus-suis
  keratitis
  uveitis
  choroiditis
Moraxella duplex (diplobacillus of Petit)
  central ulcers
H. Ducreyii
  soft chancre of lid or conjunctiva
Syphilis
  chancre of lid
  choroiditis
  optic atrophy
Keratitis (marginal) unknown etiology
Uveitis (idiopathic)

* Local therapy preferred.
† Combined intramuscular and local therapy preferred.

TABLE 4

Ocular infections in which Aureomycin probably is of no value

Erythema multiforme
  conjunctivitis
  keratitis
Ocular pemphigus
Parinaud's conjunctivitis
  leptothricosis

Pyocyaneus infection
  ulcer
Sympathetic ophthalmia
Vernal conjunctivitis
Molluscum contagiosum
Mooren's ulcer
Streptothrix concretions

period of 10 days. The corneal opacities which developed were usually minimal as compared to control cases.

Aureomycin had no effect on the virus of molluscum contagiosum.

Aureomycin was surprisingly effective in 14 cases of follicular conjunctivitis. In none of these was it possible to determine the etiology.

Six cases of vernal conjunctivitis were treated and no particular result was anticipated. It is well known that any of the antibiotics will have some tendency to give a certain degree of subjective improvement, and it is doubtful if Aureomycin will have any effect on vernal conjunctivitis.

Although one case of Parinaud's conjunctivitis due to the leptothrix was treated, no beneficial effect was anticipated because of the similarity between the leptothrix and the actinomyces from which Aureomycin is made.

In the treatment of uveitis and keratitis, it was not possible to determine in advance which patients would be improved. There is little doubt in our minds that there was marked improvement in the patients with scrofulous keratitis and scrofuloderm. There is also little doubt that the antibiotic produced improvement in several cases of uveitis of unknown etiology.

SUMMARY

Aureomycin borate has been used locally and Aureomycin HCl has been used intramuscularly in 401 patients with a wide range of ocular infections. The local use of 0.5-percent solution produced no damage to the conjunctiva or cornea.

This antibiotic was found to be effective against some of the Gram-positive cocci and several Gram-negative bacilli. It was also found to be an effective therapeutic agent in inclusion conjunctivitis and in herpes simplex of the cornea.

Its therapeutic effect in epidemic keratoconjunctivitis will require further investigation before results can be evaluated. It is, however, more effective in epidemic keratoconjunctivitis than any of the other antibiotics or drugs tried.

The intramuscular administration of Aureomycin HCl did not give rise to any toxic reactions and in only one individual was any general effect noted. The patient developed a secondary anemia which was easily controlled by the administration of iron.

The HCl is somewhat irritating on intramuscular injection, but this irritation can be controlled by the addition of a small amount of procaine hydrochloride.*

There is some indication that Aureomycin may be a valuable antibiotic in the treatment of uvetitis.

Aureomycin has a wide spectrum of activity in ocular infections.

635 West 165th Street (32).

* Because of the pain associated with intramuscular Aureomycin, since this report most of the antibiotic has been given intravenously without pain or side effects.

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DISCUSSION

DR. PHILLIPS THYGESON (San Jose, California): I realize that Aureomycin has not been available for general use. I begged a small supply of it from Dr. Braley and Dr. Sanders for a case of bilateral tuberculous keratitis which had responded temporarily

to streptomycin but had subsequently re-
lapsed, and I am very happy to say that this
man's keratitis quieted down very rapidly
on 40 mg. a day and that his vision has im-
proved in one eye from 20/100 to 20/50, and
in the other eye from hand movements to
20/70.

I used Aureomycin topically in one other
case, that of a nurse with what we considered
to be an epidemic keratoconjunctivitis, prior
to onset of corneal lesions. She had been ex-
posed to a known case of epidemic kerato-
conjunctivitis and had the preauricular

adenopathy, follicle formation, and mono-
nuclear cell exudate typical of epidemic
keratoconjunctivitis.

The borate was administered topically
only. The patient failed to develop any
corneal signs and the course was much
milder than in any of the previous cases we
had studied.

DR. BRALEY (closing) : I would like to
thank Dr. Thygeson for his remarks. I am
extremely enthusiastic about this material
and feel that it would certainly justify wide
trial when and if the material is available.

UVEITIS AND TOXOPLASMIN SENSITIVITY*

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During an experimental and clinicopath-
ologic study of toxoplasmosis, a skin testing
antigen (toxoplasmin) has been developed[1]
providing a basis for a relatively rapid and
accurate diagnosis of past and chronic[2] in-
fection with toxoplasma. This paper serves
as a preliminary report on studies of patients
with uveitis, designed to draw further at-
tention to an etiologic entity more prevalent
than generally suspected. Previous studies
of ocular toxoplasmosis, such as those of
Koch, Wolf, Cowen, and Paige,[3] Heath and
Zuelzer,[4] and of others,[4a] dealt with histo-
pathologic aspects of the infection. Vail,
Strong and Stephenson,[5] Heidelman,[6] John-
son,[7] and others[7a-e] investigated patients
with chorioretinitis for the presence of neu-
tralizing antibodies to toxoplasma, as demon-
strated by the rabbit test of Sabin and Ruch-
man.[8]

The toxoplasmin skin test served as diag-

nostic agent in the study reported here. It
was controlled by the use of (a) the toxo-
plasma neutralizing antibody test (on the
rabbit skin), (b) the toxoplasma comple-
ment-fixation test[†, 9, 10] and (c) a survey of
toxoplasmin sensitivity in two groups of in-
dividuals without eye diseases, selected for
their age only. A detailed evaluation of the
results obtained by the use of these tests and
correlation with the clinical syndromes ex-
hibited by patients will be reported in a more
extensive publication. Suffice it to say that
the skin test proved to be simpler and more
reliable than the other two tests used.[‡, 1]

† Performed by Dr. Carl M. Eklund and Dr.
David B. Lackman, both of the Rocky Mountain
Laboratory, Hamilton, Montana.

‡ Recently Sabin and Feldman[11] described a sero-
logic test for toxoplasma antibody, employing dyes
as microchemical indicators, which is more infor-
mative than the more easily performed skin test.
Their new test provides quantitative data in all
stages of the disease; whereas, the results of the
skin test are qualitative only and its main useful-
ness is in chronic toxoplasmosis (uveitis) and in
surveys.

CLINICAL STUDIES

The majority of the patients with uveitis were seen in the eye clinic of the University of California Hospital, San Francisco, where a study on the etiology of uveitis, supported by the Francis I. Proctor Foundation for Research in Ophthalmology, was being conducted. As part of that study patients' sera were submitted for serologic tests for syphilis. Brucellergin tests were performed and,

mal individuals. Hence, evaluation of data not pertaining to toxoplasmosis will be deferred.

The results of toxoplasmin tests conducted in 1947 and 1948 on groups of patients with chorioretinitis and anterior uveitis, and on two control groups of young healthy individuals and of older hospital patients with cardiac or neoplastic diseases, are presented in Table 1.

TABLE 1

TOXOPLASMIN SENSITIVITY

Grouping	Years of Age	Total No.	Numbers		Percent	
			Pos.	Neg.	Pos.	Neg.
Patients with chorioretinitis	Mean 23	28	20	8	71	29
Patients with anterior uveitis	Mean 35	40	13	27	33	67
Mothers of toxoplasmin-positive patients		8	8	0	100	0
Young healthy individuals	20–35	50	5	45	10	90
Older hospital patients	50–83	50	14	36	28	72

when positive, were followed up by agglutination and complement-fixation tests with Brucella antigen. Tuberculin, coccidioidin, histoplasmin, and Frei tests were also done routinely and, occasionally, the Kveim test for sarcoidosis was carried out.

None of the patients revealed any data as to previous illness, residence, or animal contacts that could be correlated in respect to toxoplasmosis. Apart from the tests for toxoplasmosis, enumerated above, electroencephalograms, skull roentgenograms, and psychometric studies were made on many toxoplasmin-positive patients.

Relatively few of the tests for diseases other than toxoplasmosis were positive. Certain patients had a history, with physical signs as well as laboratory evidence, of syphilis; others had lymph-node biopsies and radiologic findings suggestive of sarcoidosis. In only one of the toxoplasmin-positive patients with chorioretinitis and taboparesis, were significant dual etiologic factors uncovered. In addition to the statistically small and scattered number of positives that implicated other etiologic factors, evaluation of such tests was made difficult, since they had not as yet been conducted on groups of nor-

CHORIORETINITIS (GRANULOMATOUS POSTERIOR UVEITIS)

The incidence of toxoplasmin sensitivity in patients with chorioretinitis was 71 percent as compared to an incidence of 10 percent in a group of healthy individuals of similar age. Although the mean age of toxoplasmin reactors with chorioretinitis when first seen was 23 years, their mean age when the disease was first noted was 13 years. This contrasts with an average of 28 years, for both date of onset and when first seen, in toxoplasmin-negative patients with chorioretinitis. The high incidence of toxoplasmin sensitivity in this group is considered very significant. The actual difference between the incidence of toxoplasmin positivity in patients with chorioretinitis and the control group is 5.5 times the standard error of the difference.*

* The following formula to test for significance of the difference between proportions was used:

$$\sigma_{D\%} = \sqrt{ pq \left(\frac{1}{N_1} + \frac{1}{N_2} \right) }$$

where p is the total percentage of occurrence
$q = 1 - p$
$N_1 =$ number in first sample
$N_2 =$ number in second sample

ANTERIOR UVEITIS

Although the incidence of toxoplasmin sensitivity (33 percent) in this group exceeds the incidence in the control group (10 percent) of comparable age, the difference is not as great as in the patients with chorioretinitis. A breakdown of positive and negative reactors according to the type of uveitis is presented in Table 2.

TABLE 2

TOXOPLASMIN REACTION IN PATIENTS WITH ANTERIOR UVEITIS

Skin Test		Numbers	
		Granu-lomatous	Nongranu-lomatous
Positive	13	10	3
Negative	27	15	12
Total	40	25	15

The predominance of granulomatous (10 cases or 77 percent) over nongranulomatous anterior uveitis (3 cases or 23 percent) in the toxoplasmin positive group and the relative scarcity of positive skin tests in the nongranulomatous group of patients (only 3 out of 15 cases, or 20 percent), suggest certain correlations. The actual difference between the incidence of toxoplasmin sensitivity in the patients with granulomatous anterior uveitis and the normal control group is 3.06 times the standard error of the difference. Comparing the nongranulomatous and the control groups the difference is not significant.

Wood[13] presents evidence "that in granulomatous uveitis the various recognized, specific etiologic agents are present in living form in the uveal tract," associated with a bacterial type of hypersensitivity. In nongranulomatous uveitis a sensitization without infection of ocular tissues, which may be either bacterial or both anaphylactic and bacterial, is thought to be present.

As will be further discussed below, in toxoplasmic uveitis, organisms are likely to be present within the uveal tract. This further supports the statistical evidence in favor of a toxoplasmic etiology in 10 out of 25

cases, or 40 percent of all patients with granulomatous anterior uveitis. According to the interpretation of the survey, a small majority of patients with granulomatous anterior uveitis and most of the patients with nongranulomatous uveitis must be assigned an etiology other than toxoplasmosis for their ocular disease.

OTHER GROUPS

The frequent concurrence of positive tests for toxoplasmosis in young patients and their mothers has frequently been noted. Their similar habitat with equal chances for exposure may account for these instances, while transmission of the infection from mother to infant in utero has also been observed.

The increased incidence with age of toxoplasmin sensitivity in the general population is noteworthy and suggests that infection is contracted throughout life. None of the 19 positive individuals in the control group and none of the 8 mothers had uveitis. Only one young man had a history of an obscure disease with a rash and encephalitic symptoms when aged 21 years. In general, the impression is gained that more damage may be produced if toxoplasmic infection occurs in the young; whereas, in older individuals asymptomatic infection appears to be the rule.

SEX DISTRIBUTION.

Comparison of toxoplasmin sensitivity in males and females is presented in Table 3. Patients with chorioretinitis and anterior uveitis are listed as in Table 1, the grouping "Mothers of toxoplasmin positive patients" has been omitted, and the control group consists of individuals without eye disease, without regard to age, essentially a merging of the two control groups of Table 1.

In the control group, 24 percent of women but only 16 percent of men were toxoplasmin positive. Again, among patients with chorioretinitis, more women reacted to toxoplasmin (82 percent) than did men (55 percent). There were more than twice as many toxo-

plasmin sensitive women (14, or 70 percent) than men (6, or 30 percent) with chorioretinitis. Patients with anterior uveitis showed the reverse relationship. The numbers recorded here merely indicate a trend; they are not large enough to be statistically significant.

induration appear 24 to 72 hours after injection of toxoplasma antigen. Histologically, there is vascular damage, with exudation of fluid and cells, sometimes accompanied by necrosis, if the amount of antigen is large.

Chorioretinitis is thought to be due to the rupture of a pseudocyst in the retina, which

TABLE 3

SEX DISTRIBUTION OF TOXOPLASMIN SENSITIVITY

Group of Patients	Skin Test	Total No.	Numbers		Percent	
			Males	Females	Males	Females
Chorioretinitis	Positive	20	6	14	55	82
	Negative	8	5	3	45	18
	Total	28	11	17	100	100
Anterior uveitis	Positive	13	8	5	42	24
	Negative	27	11	16	58	76
	Total	40	19	21	100	100
Control	Positive	22	10	12	16	24
	Negative	90	53	37	84	76
	Total	112	63	49	100	100

TREATMENT

PATHOGENESIS OF TOXOPLASMIC UVEITIS

In another paper[2] the pathogenesis of toxoplasmosis was discussed. For the purpose of developing a rationale for the treatment used, it is essential here only to keep in mind the persistence of organisms long after the acute infection. This has been proven visually and by isolation in animals[12] and it is likely to occur also in man, judging from autopsy observations.[17]

Toxoplasma in both man and animals has been found in so-called "pseudocysts," which have a definite cyst wall that is argyrophilic. Such pseudocysts or cysts may lie dormant for long periods of time in the brain as well as in the eye as indicated by the lack of host reaction to their presence. If such a cyst ruptures, organisms and soluble antigen are released and the resulting tissue reaction is characteristic of the delayed (bacterial) type of hypersensitivity.[12]

This hypersensitivity reaction is also the basis for the skin test, where erythema and

is accompanied by an intense hyperergic inflammatory reaction. Pseudocysts have been seen in the retina of patients with subacute toxoplasmosis at autopsy, and in both retina and iris of experimental animals with chronic toxoplasmosis.[12]

Due to the relative poverty of humoral antibody in the neuro-ectodermal tissues and fluids (associated with the blood—neuro-ectodermal barrier for protein), much time passes before organisms and antigen released by the pseudocyst can be neutralized or phagocitized. Treatment was aimed, therefore, at increasing the antibody level in the blood and intercellular fluid by injections of carefully graded and increasing doses of toxoplasma antigen. The greater amount of available free antibody may then be capable of binding and neutralizing the antigen in the intercellular fluids, thereby minimizing the intensity of the same reaction taking place on the more vulnerable cell surfaces.

INDICATION FOR TREATMENT USED

Such toxoplasma antigen injections have

been given to patients with chorioretinitis who were toxoplasmin positive and who showed active chorioretinitis, usually accompanied by vitreous exudate. In these patients the correlation between the eye lesions and toxoplasmin sensitivity was deemed significant and no definite evidence of other etiology was uncovered. One patient was treated who suffered with both chorioretinitis and a granulomatous anterior uveitis. She also had a positive tuberculin test, but without evidence of chest disease, and had been treated unsuccessfully with tuberculin for several years. No patient with anterior uveitis alone was treated since the correlation between toxoplasmin sensitivity and the granulomatous eye lesions was not made until later.

Since nonspecific protein therapy is thought to increase the shedding of antibody into the blood stream, intravenous typhoid bacterin injections were frequently used in conjunction with toxoplasma antigen.

Although sulfonamide therapy suppresses toxoplasmic proliferation, it was not considered useful in the cases under study. The chorioretinal lesions are thought to be due more to the liberated antigen, which does not quickly diffuse out of the interstitial fluid and vitreous, than due to proliferation of toxoplasma within the retina. Actually, sulfonamide therapy had been given to several patients before they were seen by me. In no case did the referring physician note any improvement of the lesions that could be attributed to that therapy.

TECHNIQUE OF TREATMENT

After the initial toxoplasmin skin test, every patient who appeared to fufill the indications for treatment was informed as fully as possible (or the parents, in case of a minor) of the experimental nature of the treatment contemplated. This was instrumental in securing full coöperation of all patients and gained their enthusiasm for repeated venipunctures to follow antibody levels.

Depending on the amount of redness and induration developed in the skin test, a dose was chosen between one tenth and one hundredth of the skin test dose to commence potentially immunizing, intradermal antigen injections (desensitization). It was desired to keep the resulting skin reactions under 10 millimeters of redness with a minimum of induration. These injections were given twice weekly and the dose of antigen was increased as tolerated. At every visit the visual acuity was determined and the fundus was visualized, while fundus photographs or drawings and visual field measurements were made at irregular intervals to record the changes occurring.

RESULTS OF TREATMENT

Of the 9 patients treated by toxoplasmin injections, the lesions became inactive during treatment in 8 as indicated by disappearance of the vitreous exudate, decreased retinal edema and infiltration, and beginning pigment deposition. One of these patients was treated for nearly a year until the acute perimacular lesions became quiescent and started to become pigmented.

A 9th patient, who had both chorioretinitis and a granulomatous iridocyclitis, associated with a positive tuberculin test, did not improve during 6 weeks of toxoplasma antigen and typhoid bacterin injections and her anterior uveitis became more severe during that period. Subsequently, she had a course of treatment consisting 2 gm. each of sulfadiazine and sulfamerazine and paracentesis of the anterior chamber daily for 10 days, followed by 1 gm. streptomycin daily for a month. Neither of the therapeutic regimes was accompanied by improvement of the uveitis. Previously, she had had a course of penicillin injections and tuberculin therapy, likewise without effect.

Since the course of the lesions cannot be predicted, any improvement in the 8 patients, occurring during treatment, cannot necessarily be ascribed to it. The results of this experimental treatment are recorded here to

point a way for careful and prolonged clinical research work, which should be controlled by the immunologic and serologic tests for toxoplasmosis already mentioned.

DISCUSSION

SPECIFICITY OF THE TOXOPLASMIN SKIN TEST

Comparison of toxoplasmin sensitivity in normal guinea pigs and in those with chronic, latent toxoplasmosis showed a high degree of specificity for the test. These findings were supported by a significant degree of correlation between skin hypersensitivity and the presence of toxoplasma neutralizing antibodies in man.[1] Further confirmation was obtained by the anamnestic appearance or the rise of complement-fixing and neutralizing antibodies, following injection of the skin test antigen into indivdiuals exhibiting dermal hypersensitivity. The high incidence of toxoplasmin sensitivity in patients with chorioretinitis and in the mothers of such patients is significant.

Due to its wide host range Toxoplasma is a unique protozoan organism. No related organisms are known, and hence no information is available as to possible cross-reactions of dermal hypersensitivity, such as between the two fungus diseases of histoplasmosis and coccidioidomycosis and their respective skin-testing antigens.

ETIOLOGY OF UVEITIS

Reviewing the literature on uveitis[14] many causal factors have been listed. The importance attributed to each parallels to some degree the history of recognition of rheumatism, gout, tuberculosis, syphilis, focal pyogenic infections, gonorrhea, brucellosis, and sarcoidosis[15] as etiologic and clinical entities. This study, therefore, may merely reflect the enthusiasm kindled by the discovery of another "new" disease.

However, in following Woods,[13] the patients under study have been classified as having either granulomatous or nongranulomatous uveitis. Furthermore, they were subdivided as having predominantly either anterior or posterior uveal tract lesions. The results of this survey show a high incidence (71 percent) of toxoplasmin sensitivity in patients with granulomatous posterior uveitis (chorioretinitis) and a lesser, but still elevated, incidence of positivity among patients with granulomatous anterior uveitis (40 percent).

Control groups of individuals of comparable age (20 to 35 years) showed a 10-percent incidence of toxoplasmin sensitivity. A seven-fold greater incidence was found in the patients with chorioretinitis (mean age 23 years) and a four-fold greater incidence in the patients with granulomatous anterior uveitis (mean age 35 years). While these data proved statistically significant (5.5 and 3 times the standard error), no significant correlation was found between dermal hypersensitivity to toxoplasmin and the occurrence of nongranulomatous uveitis.

The findings reported here on the concurrence of chorioretinitis and toxoplasmosis are in general agreement with those made by Heidelman[6] and Johnson.[7] A comparison with the detailed studies on uveitis by Woods and Guyton[14,15] is difficult to make, since they did not distinguish in their tables between predominantly anterior and posterior uveal tract involvement, nor between granulomatous and nongranulomatous lesions.

Diagnosis made by exclusion of other known etiologic factors, or on the basis of a positive tuberculin test or a calcified pulmonary focus, or from the results of a therapeutic test with tuberculin may easily be fallacious. At the time that their studies were made, much less was known about the incidence of toxoplasmosis and perhaps also about the incidence of sensitivity to tuberculin and other antigens in the population as a whole.

It is felt, therefore, that, in this study, by suitable differentiation of clinical syndromes and by integration with controlled experimental data, two groups of patients have been singled out, a significant proportion of

whom may be assigned toxoplasma as the etiologic agent of their uveal tract lesions. Further serologic studies being carried out at present may serve to distinguish between active and inactive chronic toxoplasmosis.[11]

SUMMARY

1. Toxoplasmin, a skin test antigen made from toxoplasma, evokes reactions of a delayed (tuberculin) type of hypersensitivity in certain individuals.

2. The incidence of toxoplasmin sensitivity was 10 percent in a group of young healthy individuals and 28 percent in a group of older hospital patients with cardiac or neoplastic diseases.

3. Of 28 young patients with chorioretinitis 20, or 71 percent, were sensitive to toxoplasmin.

4. Among 40 young patients with anterior uveitis, 13, or 33 percent, were toxoplasmin sensitive. The incidence was 40 percent for the granulomatous cases and only 20 percent for the nongranulomatous cases.

5. The incidence of toxoplasmin sensitivity was higher in women than in men both in the control and the chorioretinitic group of patients.

6. Reasons for assuming a toxoplasmic etiology for a certain percentage of granulomatous uveitis cases are given. The pathogenesis of toxoplasmic uveitis is discussed, as well as the rationale, indications, technique, and results of treatment with toxoplasma antigen.

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DISCUSSION

DR. PARKER HEATH (Boston, Massachusetts): I think this is a very interesting and important paper. One suggestion of importance from the paper is that it offers another breakdown in the group of unknown causes of uveitis.

Gabriel Steiner sometime ago reported a direct relationship between the active lesion and the breaking of the pseudocyst wall and the free parasite.

DR. LORAND V. JOHNSON (Cleveland, Ohio): I have enjoyed this very much. It seems to me that this has been one of the big years in the increasing knowledge of toxoplasmosis.

Dr. Leslie Alm in Sweden has described a nutrient embryo test for toxoplasmosis, as well as a method for growing the organisms on the chick embryo. I understand that Sabin has a new sensitive skin test, using an antigen obtained from the chorion-allantoic membrane, as well as a new methylene-blue test, whereby the cytoplasm of the organism will take up methylene blue and thus be stained deeply when untreated or when treated with normal sera. If it is treated with serum from a patient with toxoplasma infection, the organism loses its affinity for methylene blue and will not stain (will soon be published in *Science*).

I hope that in your publication you will describe your method of producing toxoplasmin.

DR. FRENKEL (closing): In answer to Dr. Heath's question, vitreous exudates were almost always associated with active chorioretinal lesions and they disappeared during subsidence of the lesion during treatment, whether it was due to it or not. It is too early to say whether the treatment had any effect. However, according to the judgment of clinicians who are well acquainted with the natural history of uveitis, treatment seemed to be accelerating subsidence.

The diagnosis of chorioretinitis due to toxoplasmosis was made on the basis of skin tests, and the neutralizing antibody tests. We did not biopsy any eyes and, therefore, could not demonstrate organisms. These are all chronic cases in whom organisms are sparse. An enucleation has been done by Dr. Fry (published together with Dr. Schwartz in the new journal *Pediatrics*) and no organisms were found histologically.

Steiner and Kaump,[16] to whom you refer, showed that there is a cellular reaction to the presence of extracellular proliferative forms, such as are present in the subacute and the acute disease. They did not talk of pseudocysts as far as I can determine. Most authors do not differentiate between intracellular proliferative forms and pseudocysts

of toxoplasma, since they are not aware of the argyrophilic cyst wall. I have found the latter to be present in three strains of toxoplasma which I carry and undoubtedly it is a significant structure. The cyst walls of Coccidioides immitis spherules and the cyst walls of the rabbit coccidium Eimeria stiedae stained similarly with Wilder's silver stain. However, this does not imply a relationship between these organisms.

An account of the production of toxoplasmin has been published.[1] There is no great difficulty in preparation of the antigen.

Dr. Johnson's exhibit, showing some of Dr. Alm's technique, is very interesting. The latter is probably an improvement of the neutralizing antibody technique, since it lends itself better to statistical analysis. As may be inferred from one of my lantern slides, differentiation between positive and negative neutralization tests is not always easy to make. I am looking forward with great interest to the results obtainable with the new dye test, which, as Dr. Sabin mentioned to me, is beginning to show much promise.

EXPERIMENTAL STUDIES WITH ANTIBIOTICS*

BACITRACIN, STREPTOMYCIN, PENICILLIN, AND ANTIBIOTIC MIXTURES IN INTRAOCULAR INFECTIONS WITH PENICILLIN-RESISTANT STAPHYLOCOCCI

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Pathogenic Staphylococcus aureus is one of the most frequent etiologic agents in postoperative and posttraumatic purulent endophthalmitis.

In 1943, von Sallmann[1,2] demonstrated that experimental intraocular infections in rabbits, caused by *penicillin-sensitive* staphylococci, responded favorably in a high percentage of cases to local treatment with penicillin iontophoresis.

However, from 10 to 38 percent of staphylococci, isolated from clinical sources, have variously been reported by different authors to be relatively resistant to penicillin;[3-9] and some authorities believe that this frequency will increase.[9,10]

The purpose of this study, therefore, was to investigate the comparative values of various antibiotics (penicillin, streptomycin, and bacitracin) and antibiotic mixtures (penicillin-sulfacetimide, penicillin-streptomycin,

streptomycin-sulfacetimide) in the local treatment of experimental intraocular infections caused by *penicillin-resistant* staphylococci.

Leopold and Nichols[11] reported finding high concentrations of streptomycin in the aqueous of normal rabbit eyes, following iontophoresis; and this finding was confirmed by Bellows and Farmer.[12]

Bacitracin, discovered by Meleney and coworkers,[13] is one of the newer antibiotics. Having an antibacterial spectrum very similar to that of penicillin, it has given good results in the local treatment of surgical infections caused by penicillin-resistant staphylococci.[7] No reports have yet appeared concerning its use in ophthalmology.

Conflicting results have been reported on the effects of combined chemotherapy,[14-21] but the majority of investigators have observed synergistic or additive activity.

The high solubilty of sodium sulfacetimide, at a neutral pH, makes it a satisfactory sulfonamide for use in mixtures with antibiotics. It reaches the aqueous in high concentrations, following iontophoresis;[2,22] and

it is effective against staphylococci and other sulfonamide-sensitive organisms in conjunctival and corneal infections.[23-26]

The feasibility of applying combined chemotherapy to the eye by iontophoresis was demonstrated by von Sallmann,[2] who found approximately the same concentrations of penicillin and sulfacetimide in rabbit aqueous after iontophoresis with solutions containing both their sodium salts, as after iontophoresis with solutions containing the respective salt alone.

Preliminary experiments were carried out

The eyes were examined during the course of the instillations and 15 hours following the last one.

Results. A concentration of 5,000 units per cc. was very irritating and caused marked chemosis, conjunctival congestion, and belpharospasm, but no corneal damage, in all eyes, commencing soon after the first instillation (Table 1).

A concentration of 1,000 units per cc. was relatively well tolerated, but did cause a mild conjunctival congestion and a very slight degree of chemosis in 8 out of 11 eyes.

TABLE 1

EFFECTS OF SIX TO SEVEN HOURLY INSTILLATIONS OF BACITRACIN SOLUTIONS IN NORMAL RABBIT EYES

Lot No.	Units per mg.	Concentration (U/cc.)	Solvent	No. of Eyes	Ocular Reaction	
					Immediately after Last Instillation	15 Hours after Last Instillation
B130	25	5,000	Distilled water	5	Marked chemosis, conjunctival congestion and blepharospasm; no corneal damage.	
B471212S	50	5,000	Distilled water	3		
B471212S	50	5,000	Normal saline	3		Lids, conjunctivas, and cornea essentially normal.
B130	25	1,000	Distilled water	5	Mild conjunctival congestion; very slight chemosis in 8 of 11 eyes.	
B471212S	50	1,000	Distilled water	3		
B471212S	50	1,000	Normal saline	3		

to determine the irritability and penetrability of bacitracin in the normal rabbit eye, and to determine if any chemical or therapeutic incompatibilities existed between the antibiotics which we wished to use in therapeutic mixtures.

IRRITABILITY OF BACITRACIN

I. INSTILLATION OF DROPS

Technique. Three drops of bacitracin solution were instilled into the conjunctival sacs of 22 normal rabbit eyes, every hour, for 6 to 7 instillations, using two different concentrations (5,000 units per cc. and 1,000 units per cc.), two different solvents (distilled water and normal saline), and two different lots (No. B130, prepared in September, 1947, containing 25 units per mg.; and No. B471212S, prepared in January, 1948, containing 50 units per mg.).

The findings were the same for both lots and for both solvents.

Fifteen hours following the last instillation, all eyes had returned to normal.

Comment. Among the factors influencing the irritability of ophthalmic solutions are pH and tonicity. The pH of these solutions was 6.5 to 6.8. Fifteen hundred units per cc. of the lot containing 25 units per mg. was approximately isotonic with normal saline.[35]

Johnson[25] found the nephrotoxicity of bacitracin in mice to be very much less when the antibiotic was dissolved in saline, but the reason for this was not understood. The possibility existed that sodium chloride might neutralize some toxic component of the bacitracin. The use of normal saline as solvent in our experiments, however, did not lessen the irritability of the drug to the eye.

II. CORNEAL BATH AND IONTOPHORESIS

Technique. Aqueous solutions of bacitracin in three different concentrations (5,000 units per cc., 2,500 units per cc., and 1,000 units per cc.) were applied for 5 minutes by corneal bath and iontophoresis (cathode on the eye; current at 1.6 ma.) to 40 normal rabbit eyes, after local anesthesia with 0.1-percent nupercaine solution. Twenty-four hours later, the corneas were stained with 2-percent sodium fluorescein and studied.

Results. Using a concentration of 5,000 units per cc., a single corneal bath or iontophoretic application for 5 minutes produced extensive corneal abrasions in all eyes (5 eyes by each method).

Using a concentration of 2,500 units per cc., a single corneal bath or iontophoretic application for 5 minutes produced corneal abrasions in a majority of cases (3 out of 5 eyes, and 4 out of 5 eyes, respectively).

With a concentration of 1,000 units per cc., however, repeated applications were well tolerated, providing that the intervals between applications were not less than 9 to 12 hours. If the intervals were reduced to 5 hours, two consecutive applications produced corneal abrasions in most cases (corneal bath : 3 out of 5 eyes; iontophoresis : 4 out of 5 eyes). In every case of iontophoresis, a transient haziness of the corneal epithelium was observed immediately following the application. This was similar, but denser, than that seen after penicillin iontophoresis.

Comment. These findings limit the concentration of bacitracin that can be applied to the rabbit eye, by any of the three types of administration tested, to 500 to 1,000 units per cc. The practical, therapeutic significance of this is discussed later.

PENETRABILITY OF BACITRACIN

Technique. Under 0.1-percent, local nupercaine anesthesia, a concentration of 1,000 units of bacitracin per cc. of distilled water was applied for 5 minutes by corneal bath and by iontophoresis (cathode on the eye;

current at 1.6 ma.), to 4 normal rabbit eyes, 2 determinations being made for each method of application. Aqueous was withdrawn 45 minutes later and assayed for its bacitracin content.*

Results. The concentrations in the aqueous following corneal bath were 4 units per cc. in each case (Table 2); those following

TABLE 2

CONCENTRATION OF BACITRACIN IN AQUEOUS OF NORMAL RABBIT EYE, FORTY-FIVE MINUTES AFTER APPLICATION OF 1,000 UNITS OF BACITRACIN PER CC. DISTILLED WATER AFTER 0.1 PERCENT LOCAL NUPERCAINE ANESTHESIA

Method	Rabbit	Concentration in Aqueous (Units per cc.)
Corneal bath	1	4
	2	4
Iontophoresis	3	8
	4	12

iontophoresis were 8 and 12 units per cc., respectively, or 2 to 3 times as much.

Comment. These concentrations are considerably higher than those necessary to inhibit most strains of staphylococci in vitro (about 0.5 to 1.0 unit per cc.[27]).

The differences between the concentrations obtained by corneal bath, on one hand, and by iontophoresis, on the other, are not as great for bacitracin as for the sulfonamides,[22, 29] atropine,[30] penicillin,[31] or streptomycin.[12] Greater transient damage to the corneal epithelium by bacitracin probably permits a larger proportion of that reaching the aqueous to do so by simple diffusion.

COMPATIBILITIES OF ANTIBIOTICS

I. CHEMICAL COMPATIBILITIES

Technique. Appropriate mixtures were made and observed for evidences of incompatibility.

Results. An aqueous solution containing streptomycin calcium-chloride complex,

* Miss B. Johnson of the Department of Surgical Bacteriology, College of Physicians and Surgeons, Columbia University, assayed the aqueous samples for bacitracin, and, in the experiments discussed later, carried out the bacitracin sensitivity tests.

20,000 units per cc., and 10-percent sodium sulfacetimide formed a thick insoluble precipitate, which would not disappear on heating or on raising or lowering its pH. No precipitate formed if the concentration of streptomycin calcium chloride in the mixture was 10,000 units per cc. A solution containing streptomycin sulfate, 20,000 units per cc., and 10-percent sodium sulfacetimide, remained clear.

There was no incompatibility in a mixture containing streptomycin calcium-chloride complex, 20,000 units per cc., and sodium penicillin, 1,000 units per cc.

That sodium penicillin and the sulfonamides are compatible is already well known.

Comment. Calcium is known to precipitate many anions. Chlorides on the other hand (except for those of bismuth, lead, mercury, and silver) are generally water-soluble. The incompatibility between streptomycin calcium-chloride complex and sodium sulfacetimide is probably due to the calcium cation combining with the sulfacetimide anion to form a less soluble compound, calicum sulfacetimide.

II. THERAPEUTIC COMPATIBILITIES

Waksman and his co-workers[32] reported the detrimental effects of glucose, sodium chloride, and sodium phosphate on the antibacterial activity of streptomycin; and Berkman and his colleagues[33] demonstrated a marked in vitro inhibition of the antibacterial activity of streptomycin by physiologic concentrations of sodium chloride, potassium chloride, sodium sulfate, sodium tartrate, and ammonium acetate.

In vitro experiments were, therefore, indicated to determine if any such inhibition occurred when streptomycin was combined with sulfacetimide, penicillin, or bacitracin, in the proportions which we wished to use therapeutically.

Technique. The serial dilution method employed at the Presbyterian Hospital, New York City, for testing in vitro streptomycin sensitivities, was used in these experiments.

The test organism was a streptomycin-sensitive strain of Bacillus aerogenes.

Aqueous solutions were prepared, containing: (1) Streptomycin CaCl complex, 10,000 units per cc. and 10-percent sodium sulfacetimide; (2) streptomycin sulfate, 10,000 units per cc. and 10-percent sodium sulfacetimide; (3) streptomycin CaCl complex, 10,000 units per cc., and sodium penicillin, 1,000 units per cc.; (4) streptomycin CaCl complex, 10,000 units per cc., and bacitracin, 1,000 units per cc.

The antibacterial activity of each of these mixtures was compared to that of solutions containing streptomycin, sulfacetimide, penicillin, and bacitracin, alone, and in the same concentrations as in the mixtures.

Rows of eight tubes were set up, the tubes of each row containing 2, 4, 6, 8, 10, 12, 15, and 20 units per cc. of streptomycin respectively and/or the corresponding proportional amount of the second drug being investigated.

The standard inoculum was added, the tubes were incubated for 72 hours, and then examined for evidence of bacterial growth, as determined by the presence of visible turbidity.

Results. Growth of the organisms was not inhibited by any of the concentrations of sulfacetimide, penicillin, or bacitracin, where these agents were used alone.

Growth was inhibited in all rows containing streptomycin, alone or in mixtures: in four rows, by solutions containing 6 and more units of streptomycin per cc.; and, in the remaining three rows, by solutions containing 8 and more units per cc.

Comment. The difference between inhibition by 6 units or by 8 units per cc. is negligible and has no significance, being within the limits of experimental er   of the test. The results indicate that the   was no inhibition of the antibacterial activity of streptomycin by sodium sulfacetimide, sodium penicillin, or bacitracin, in the proportions used.

Since completing these experiments, re-

ports have appeared in the literature confirming the results: Bondi and Dietz[21] reported a slight degree of synergistic or additive activity between streptomycin and penicillin, in vitro, against Staphylococcus aureus; and Klein and Kimmelman[20] found both sulfadiazine and penicillin to be synergistic with streptomycin, in vitro, against the same organism.

TREATMENT OF INTRAOCULAR INFECTIONS

Technique. A search was made for strains of pathogenic Staphylococcus aureus, resistant to penicillin, but sensitive to streptomycin and bacitracin. For this purpose, the in vitro sensitivities of a large number of strains were determined, and their ability to hemolize red blood cells, ferment mannitol, and coagulate plasma, was noted. Three such strains were found.

The technique of inoculation, described by von Sallmann,[1] was used throughout, 0.05 cc. of inoculum being injected into the anterior chamber, after extensive damage to the lens with the needle. In every instance, counts were made of the numbers of organisms injected.

Preliminary inoculations, with varying dilutions in normal saline, of 18-hour broth cultures of the three strains were first made in rabbit eyes to determine the dilutions that would give satisfactory test lesions.

Experimental intraocular infections were then produced, with the appropriate dilutions, in 115 rabbit eyes, and were treated locally by corneal iontophoresis (cathode on the eye; current at 1.6 ma.), after local anesthesia with 0.1-percent nupercaine, and commencing 4 to 6 hours after inoculation. Iontophoresis was applied for 5 minutes, twice a day, for 5 days, with intervals of at least 9 hours between successive applications. It was discontinued on any eye that perforated or became frankly suppurative. In the case of one strain (strain C), a five-minute corneal bath was given instead of the second daily iontophoresis.

The drugs* were applied, both alone and in the mixtures, in the following concentrations: sodium sulfacetimide, 10 percent; sodium penicillin, 1,000 units per cc.; streptomycin, 20,000 units per cc.; bacitracin, 1,000 units per cc. The mixtures used were: penicillin and sulfacetimide; penicillin and streptomycin; streptomycin and sulfacetimide. Streptomycin sulfate was used in the streptomycin-sulfacetimide mixture, but otherwise the calcium-chloride complex was used.

Results. The first strain (strain A) fermented mannitol, but did so slowly; it was nonhemolytic and coagulase negative. It was highly resistant in vitro to penicillin, requiring 10 units per cc. for inhibition, and had an average sensitivity to streptomycin (8 units per cc.). Injection of 0.05 cc. of a 10^{-1} dilution (1,200,000 organisms) caused self-limited infections only, in all eyes, and these were not affected by any of the solutions used.

The second strain (strain B) was hemolytic, mannitol positive, and coagulase positive. It was moderately resistant in vitro to penicillin, requiring 1 unit per cc. for inhibition. It had an average sensitivity to streptomycin (9 units per cc.) and to bacitracin (0.62 units per cc.). Injection of 0.05 cc. of a 10^{-4} dilution (900 to 1,100 organisms) produced severe suppurative panophthalmitis in all control eyes.

The results of treatment, in the case of this strain, are listed in Table 3, under three headings:

1. Excellent Results. These eyes showed signs of intraocular inflammation for 24 to 72 hours following inoculation, but were quiet by the 5th day. At this time, there was alway some organizing exudate in the anterior chamber, adhering to the anterior surface of the lens in the pupillary area (fig. 1C), which disappeared during the next two weeks, leaving the anterior chamber clear.

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* The sodium sulfacetimide for this study was kindly furnished by the Schering Corporation; the streptomycin CaCl complex by Merck and Co., Inc.

TABLE 3

EXPERIMENTAL INTRAOCULAR STAPHYLOCOCCAL INFECTIONS,* TREATMENT WITH
IONTOPHORESIS TWICE A DAY

STRAIN B†

Treatment	No. of Eyes	Results		
		Excellent	Intermediate	No Effect
Penicillin	6	6	—	—
Penicillin-sulfacetimide	6	5	—	1
Penicillin-streptomycin	6	6	—	—
Streptomycin	6	4	1	1
Streptomycin-sulfacetimide	6	1	2	3
Sulfacetimide	5	—	—	5
Bacitracin	6	—	2	4
Controls	7	—	—	7

* Inoculum: 900–1,100 organisms.

† Hemolytic, mannitol positive, coagulase positive. Inhibited by: penicillin, 1 unit per cc.; streptomycin, 9 units per cc.; bacitracin, 0.62 units per cc.

A thin linear opacity always remained in the lens, where it had been incised (fig. 1D).

2. *Intermediate Results.* These eyes responded, but less dramatically, and retained sequelae, such as synechias, pupillary membranes, and corneal opacities (fig. 1B).

3. *No Effect.* These eyes developed severe suppurative panophthalmitis (fig. 1A).

Penicillin gave excellent results in 6 out of 6 eyes when used alone, in 5 out of 6 eyes when combined with sulfacetimide, and in 6 out of 6 eyes when combined with streptomycin.

Streptomycin gave excellent results in 4

TABLE 4

EXPERIMENTAL INTRAOCULAR STAPHYLOCOCCAL
INFECTIONS,* IONTOPHORESIS ONCE A DAY,
CORNEAL BATH ONCE A DAY

STRAIN C†

Treatment	No. of Eyes	Results	
		Bene-fited	Not Bene-fited
Penicillin	6	—	6
Penicillin-sulfacetimide	6	1	5
Penicillin-streptomycin	6	1	5
Streptomycin	6	2	4
Streptomycin-sulfacetimide	3	1	2
Sulfacetimide	5	—	5
Bacitracin	4	—	4
Controls	9	—	9

* Inoculum: 1,500 to 1,700 organisms.

† Hemolytic, mannitol positive, coagulase positive. Inhibited by: penicillin, 10 units per cc.; streptomycin, 8 units per cc.; bacitracin, 0.75 units per cc.

out of 6 eyes and an intermediate result in 1 eye, when used alone. It gave an excellent result in 1 out of 6 eyes and an intermediate result in 2 eyes when combined with sulfacetimide.

All 5 eyes treated with sulfacetimide alone were lost. Bacitracin alone gave 2 intermediate results, and 4 eyes were lost.

The third strain (strain C), also hemolytic, mannitol positive, and coagulase positive, was highly resistant in vitro to penicillin, requiring 10 units per cc. for in-vitro inhibition. It had an average sensitivity to streptomycin (8 units per cc.) and to bacitracin (0.75 units per cc.). Injection of 0.05 cc. of a 10^{-4} dilution (1,500 to 1,700 organisms) produced a severe suppurative panophthalmitis in all control eyes (fig. 2A).

Table 4 lists the results of treatment in the case of this strain. Favorable responses were less numerous and not as dramatic, all eyes retaining some inflammatory sequelae (fig. 2B). None of the 6 six eyes treated with penicillin alone were benefited. Only 1 out of 6 eyes treated with the penicillin-sulfacetimide mixture responded. One out of 6 eyes treated with the penicillin-streptomycin mixture, 2 out of 6 eyes treated with streptomycin alone, and 1 out of 3 eyes treated with the streptomycin-sulfacetimide mixture also were benefited. All other eyes were lost, including 5 treated with sulfacetimide alone, and 6 treated with bacitracin alone.

Fig. 1 (Locke). Results of treatment, Strain B. (A) Control eye showing severe suppurative panophthalmitis. (B) Intermediate result, showing retained inflammatory sequelae. (C) Excellent result five days after inoculation, showing organizing exudate in anterior chamber adherent to anterior surface of lens in pupillary area. (D) Excellent results three weeks after inoculation, showing anterior chamber clear following absorption of exudate. Linear opacity remains where lens was incised.

Comment. Inoculation with 1,200,000 organisms of strain A caused mild, self-limited infections in all eyes, while inoculation with 900 to 1,100 organisms of strain B and 1,500 to 1,700 organisms of strain C resulted in severe progressive panophthalmitis in all control eyes. Thus there was a dramatic correlation between the findings of the in-vitro pathogenicity tests and the in-vivo results.

Strains of staphylococci requiring 1 unit of penicillin per cc. for in vitro inhibition are generally considered to be relatively penicillin-resistant, since injections of massive doses are required to attain these concentrations of penicillin in the blood.[34-36] The good results obtained with penicillin against strain B, however, in these intra-ocular infections are not entirely unexpected when it is realized that a concentration of penicillin as high as 2.2 to 3.3 units per cc. is obtained in the aqueous, following iontophoresis with 1,000 units per cc., for 5 minutes.[37]

In the case of this strain, it appeared to make little difference whether penicillin was used alone, or in combination with sulfacetimide or streptomycin.

Streptomycin, giving the next best results against strain B, was fairly effective. It was less effective when combined with sodium sulfacetimide, but a larger number of eyes are needed to give this finding statistical significance.

The ineffectiveness of penicillin against strain C, requiring 10 units per cc. for in-
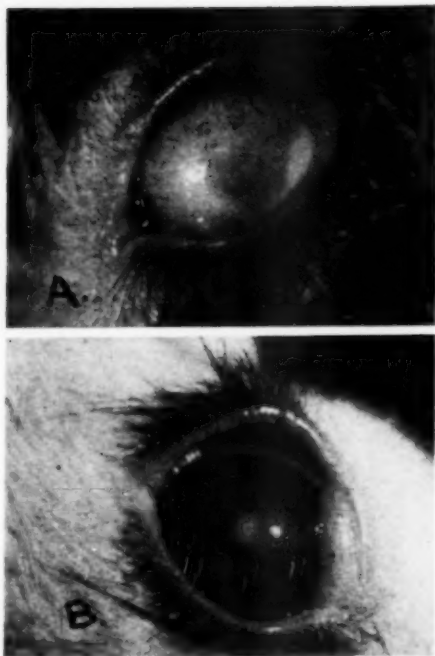
Fig. 2 (Locke). Results of treatment, Strain C. (A) Control eye, showing severe suppurative panophthalmitis. (B) Eye benefited from treatment, showing retained inflammatory sequelae.

hibition, correlates with our knowledge of penicillin aqueous levels.

Against this strain, streptomycin, apparently, was the only effective agent, since of 5 eyes benefiting from treatment, all but 1 received streptomycin, either alone or in a mixture. Even the effectiveness of streptomycin, however, was limited, since of 15 eyes receiving it, only 4, or 27 percent, responded; and the responses were not as marked as in the case of the previous strain. The fact that the second daily treatment was by corneal bath, rather than by iontophoresis, may have been the reason.

The rapid development of an intensely purulent inflammatory response suggests that the production of sulfonamide inhibitors may have been an important factor in the ineffectiveness of sulfacetimide against all strains.

Our conclusions regarding the ineffectiveness of bacitracin in these experimental intraocular infections should not be extended to exclude its possible value in other types of ocular infection. However, our findings limiting the concentrations that can be used in the eye do impose a limitation on its possible usefulness in local ophthalmic therapy. In vitro, the ratio of the antistaphylococcal activity of bacitracin to that of penicillin, in terms of units per cc. required to inhibit sensitive strains, is about 1 to 10.[27] In vivo, certain factors, such as the slower diffusion and excretion of bacitracin[39] and, in some instances, the inhibition of penicillin by penicillinase,[40-42] might effect a lowering of this ratio. But nevertheless, against organisms sensitive to both, a given concentration of bacitracin must be expected to have an antistaphylococcal activity considerably less than the same concentration of penicillin.

Bacitracin is still in the early stages of its development. Further purification, making possible the use of higher concentrations, may yet render it an effective agent in the treatment of experimental intraocular staphylococcal infections.

From a consideration of our in-vivo and in-vitro results, and the results of the in-vitro experiments by Klein and Kimmelman[20] and Bondi and Dietz,[21] the use of penicillin and streptomycin in combination would appear to be a sound therapeutic procedure, especially when an exact bacteriologic diagnosis has not been made, or if the sensitivities of the infecting organisms are not known.

SUMMARY

1. Bacitracin, in a concentration of 1,000 units per cc., is relatively well tolerated by the normal rabbit eye, but higher concentrations are irritating.

2. Therapeutic concentrations of bacitracin can be obtained in the aqueous by corneal bath and iontophoresis.

3. Sodium sulfacetimide is incompatible

with streptomycin calcium chloride in certain concentrations, but is compatible with streptomycin sulfate.

4. The antibacterial activity of streptomycin against a strain of B. aerogenes, in vitro, was not inhibited by sodium sulfacetimide, sodium penicillin, or bacitracin.

5. Penicillin was the drug of choice, over streptomycin, bacitracin, and sulfacetimide, in the local iontophoretic treatment of intraocular staphylococcal infections caused by a strain requiring 1 unit per cc. for in-vitro inhibition. Used alone, and in mixtures with streptomycin and sulfacetimide, it controlled the infection in 17 out of 18 eyes. Against a strain requiring 10 units per cc. for inhibition, it was ineffective.

6. Streptomycin was the second most effective agent. When applied twice daily, by iontophoresis, against a sensitive strain, it controlled the infection in 4 out of 6 eyes.

7. Bacitracin and sulfacetimide were of no value in these infections.

8. The use of penicillin and streptomycin in combination is a sound therapeutic procedure, especially if the sensitivities of the infecting organisms are not known.

635 West 165th Street (32).

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DISCUSSION

Dr. HOWARD P. VENABLE (St. Louis, Missouri): I would like to ask Dr. Locke if, in his experience, his work would suggest that the 30-percent sodium-sulfacetimide which is advocated by the company would be a little too irritating?

Dr. LOCKE (closing): In answer to Dr. Venable's question: I myself have never used 30-percent sodium sulfacetimide, but Dr. von Sallmann has had a great deal of experience with it, and we felt we could not go higher than a 10-percent solution for iontophoresis. Of course, the 30-percent solution is used as drops. It is considered to be too strong for iontophoresis in this concentration.

INDUSTRIAL VISION TECHNIQUES*

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INTRODUCTION

The emphasis upon vision testing in industry has shifted from primary concern for first aid following accidents to selection and classification of personnel for job placement. The value of this new approach has been demonstrated to labor and management. Better placement in industrial jobs has resulted in greater job satisfaction, increased earning power, as well as promotion and advancement in his craft for the individual worker. These results have been reflected in the reduction of overhead, wastage, and inefficient operation, which are of vital importance to management. The greater productivity of the worker, also, tends toward greater profits for industry. Finally, the detection of abnormal ocular or visual conditions is important for the health and safety of the worker.

Vision testing, which is aimed primarily at the selection and classification of personnel for special visual tasks in industry, must be administered quickly by trained technicians rather than by ophthalmologists. The development of machine vision-testing equipment has made possible the routine administration of visual tests by technicians, who do not need to know anything about the usual clinical tests of vision, and are not required to make any interpretation of the results. The machine tests are contained in a single instrument, are administered according to a standardized procedure, and are scored according to arbitrary scales.

For classification and assignment, the comparison of scores on the visual tests with criteria of performance on the job, whether these be foreman's ratings, units produced, breakage, or earnings, determine the profile of "cut-off" scores for a particular job.

Usually, the personnel department is responsible for the testing of the applicants, the validation against criteria of performance, and the establishment of the profile scores. The industrial medical department, by reference to a table of clinical equivalents, may establish certain minimum scores for referral of patients to the clinic or to outside practitioners for evaluation and treatment of the ocular condition suggested by the tests.

For job placement, it is not necessary that visual screening tests predict the results of the corresponding clinical tests. If the test predicts performance on the job, that is sufficient. However, from the clinical and safety points of view, as well as for selecting procedures for rapid military mobilization, it is desirable that the machine visual tests predict with fair accuracy the clinical measures of vision.

In order to determine the reliability and validity of the current industrial vision screening devices, a number of research projects were established in the military services.[14]

The first test of the Ortho-Rater was conducted at Fort Eustis, Virginia, an antiaircraft artillery replacement training center, in connection with the selection of stereoscopic rangefinder operators, during the spring of 1943. Although the results of this study have not been published, the prediction of visual acuity at the level of 20/20 vision was found to be very good.

The next study was conducted at the U. S. Naval Training Center, Sampson, New York, in connection with the selection of

stereoscopic rangefinder operators for the
Radar and Rangefinder School, Fort Lau-
derdale, Florida. A test-retest analysis[15] was
made of the results of 234 administrations
of the Ortho-Rater by 26 newly trained
examiners. These examiners were optom-
etrists enlisted in the Hospital Corps of the
U. S. Navy.

The results of this study, which was con-
cerned only with reliability (the coefficients
of reliability varied from 0.49 to 0.83),
emphasized the importance of careful train-
ing of the technicians who are to operate
the machine tests. The standard instruc-
tions[16] to the examinee must be memorized
perfectly, and each examinee must be en-
couraged to do his best after the examiner
is convinced that he understands the direc-
tions given on each subtest. It is important
that each examinee be treated in the same
way.

These two preliminary tests showed that
the Ortho-Rater could be used satisfactorily
for mass testing in the military situation.
The validation of the Ortho-Rater test of
depth perception for the selection of stereo-
scopic rangefinder operators has been dem-
onstrated adequately.[17]

At the U. S. Naval School of Aviation
Medicine and Research, Pensacola, Florida,
a test-retest study[12, 13, 18] of the Bausch &
Lomb Ortho-Rater and of the corresponding
clinical tests was made in 1945. This study
shows, in general, that the visual tests in-
corporated in the Ortho-Rater are as con-
sistent in the measures obtained as the clini-
cal tests. The measures of far visual acuity
agree satisfactorily with those obtained
clinically. Measures of heterophoria do not
agree closely, but, in view of the variability
of heterophoria itself, the relationship may
be as close as can be expected for any two
measures of this anomaly.

The Medical Field Research Laboratory,
Camp LeJeune, North Carolina, also re-
ported on a comparative study[5, 6] of visual
screening devices.

The most extensive studies[7, 11, 19, 20] of the
three available commercial screening devices
were conducted at the U. S. Naval Medical
Research Laboratory, Submarine Base, New
London, Connecticut. Some of the statistical
analyses of these data were undertaken by
The Adjutant General's Office in connection
with their intensive investigation of tests of
visual acuity at Fort Dix, New Jersey, in
coöperation with the Army-Navy-NRC Vi-
sion Committee.[1, 2] These statistical analyses
are incorporated in a report[3] issued by The
Adjutant General in 1947.

DISCUSSION OF RESULTS

The results of the evaluation of the vari-
ous machine vision-testing devices, which
are discussed in this paper, have been taken
from the various aforementioned reports
and the sources are acknowledged in the
various tables or charts and in the list of
references.

The test-retest reliability of the various
instruments is indicated by the coefficients
of correlation presented in Table 1. In gen-
eral, the coefficients of this table show that
the Ortho-Rater provides the most consistent
measures and the Telebinocular the least con-
sistent.

For far and near lateral phoria, the co-
efficients range from 0.75 to 0.92, and the
instruments are more nearly equivalent. It
should be noted that the reliabilities of the
clinical measures are of the same order of
magnitude.

For monocular far acuity, the Ortho-
Rater and Sight-Screener are practically
equal in consistency, the coefficients ranging
from 0.81 to 0.90. The Telebinocular is only
slightly less good in this aspect with co-
efficients ranging from 0.78 to 0.86. Only in
the Pensacola study did the clinical measure
of far monocular acuity appear to be more
reliable than a machine test.

For the near tests of acuity, both binocu-
lar and monocular, the consistency of the
Ortho-Rater is noticeably greater than that
of the other two instruments.

The reliabilities of measures of far ver-

TABLE 1

COEFFICIENTS OF RELIABILITY OF TESTS*

Test	Ortho-Rater	Sight-Screener	Telebinocular	Clinical
Far vertical phoria	0.79	0.61	0.63	0.64
Far lateral phoria	0.87	0.80	0.75	0.81
Binocular far	0.88–0.93	0.70	—	0.81–0.97
Monocular far	0.81–0.90	0.84	0.78–0.86	0.80–0.97
Depth	0.83	0.57	0.79	0.62–0.72†
Binocular near	0.84–0.87	0.70	0.72	0.67
Monocular near	0.80–0.90	0.77	0.71	0.75–0.78
Near vertical phoria	0.73	0.55	—	0.74
Near lateral phoria	0.81–0.92	0.83	0.85	0.90

* The data for this Table were selected from the Pensacola (N = 100), New London (N = 128) and the Adjutant General's Office Report No. PRS No. 742. See references 3, 7–13.
† The Howard-Dolman test.

tical phoria by the Sight-Screener, Tele-binocular, and clinical tests are equivalent, 0.61 and 0.64, while that of the Ortho-Rater is much higher, 0.79. For near vertical phoria, the reliabilities of the Ortho-Rater and clinical measures are equivalent, 0.73 and 0.74, while that for the Sight-Screener is much lower, 0.55.

In the measures of depth perception, the Ortho-Rater and Telebinocular are nearly[14] equivalent as to reliability, 0.83 and 0.79, whereas the Sight-Screener and Howard-Dolman test are somewhat less consistent, 0.57 and 0.62 to 0.72.

The results of all tests on the instruments were compared with the clinical ophthalmic tests. The coefficients of correlation are presented in Table 2.

For far and near monocular acuity, the coefficients for the Ortho-Rater and Sight-Screener are approximately 0.75, while those for the Telebinocular are approximately 0.55.

The Ortho-Rater appears to provide a much better measure of far lateral phoria, r = 0.57 to 0.70, as compared with the other two instruments, r = 0.37 for each. For near lateral phoria, however, the three instruments are practically equivalent: Ortho-Rater, 0.67 to 0.77; Sight-Screener, 0.54; and Telebinocular, 0.68.

For all instruments the coefficients of correlation for vertical phoria are relatively low, ranging from 0.29 to 0.50.

The only comparison in measures of depth perception is between the Ortho-Rater and the Howard-Dolman test. These coefficients (0.59 to 0.62) are no greater than those

TABLE 2

RELATIONSHIPS* BETWEEN INSTRUMENTS AND CLINICAL OPHTHALMIC EXAMINATION

Test	Ortho-Rater	Sight-Screener	Telebinocular
Far vertical phoria	0.29–0.49	0.28	0.43
Far lateral phoria	0.57–0.70	0.37	0.37
Binocular far	0.79–0.90	0.71	—
Monocular far	0.72–0.84	0.74	0.58
Depth	0.59–0.62†	—	—
Binocular near	0.70	0.64	0.55
Monocular near	0.75	0.71	0.55
Near vertical phoria	0.34–0.50	0.34	—
Near lateral phoria	0.67–0.77	0.54	0.68

* The data for this Table were selected from the Pensacola report (N = 100), New London report (N = 128) and The Adjutant General's Office Report No. PRS No. 742. See references 3, 7–13.
† Howard-Dolman test.

TABLE 3

FACTOR LOADINGS OF FAR VISUAL ACUITY TESTS[*]

Instrument	Resolution	Accommodation	Form	Interference
Snellen Chart	0.70 0.86	0.00 0.12	0.24 0.50	0.01 0.11
Ortho-Rater	0.77 0.86	−0.07 0.07	0.00 0.11	0.23 0.52
Sight-Screener	0.75 0.90	0.06 0.20	0.02 0.26	0.06 0.18
Telebinocular	0.62 0.72	0.15 0.25	0.02 0.07	0.01 0.23

[*] The Adjutant General's Office PRS Report No. 742, August, 1947, p. 54.

generally found between any two tests of depth perception.[*]

A statistical study of the New London data[*] on the comparison of three commercial visual screening devices was conducted by The Adjutant General's Office, using the method of factor analysis. The data of Tables 3 to 7 have been extracted from this report.[3]

For the purpose of this paper a factor loading can be described as the coefficient of correlation between the test and a specific factor. The square of the factor loading represents the proportion of the total variability of the specific test scores which is explained by the factor. This factor is named after careful consideration of the character of the test and the distribution of all factor loadings.

In Table 3 it is shown that the factor loadings for resolution in the far visual

acuity test for the Snellen Chart, the Ortho-Rater, and Sight-Screener are of the same order of magnitude, while those for the Telebinocular are slightly lower. It is shown, further, that a part of the variability of the test scores on the Snellen Chart and Sight-Screener can be attributed to a form factor which is not effective with the other two instruments. The variability of scores on the Ortho-Rater can be attributed in part to a specific interference or machine factor. This might be eliminated by an improvement of the instrument or test targets. The Telebinocular shows both accommodation and machine factors, and represents the least pure test of retinal resolution.

For the near-vision tests the factor loadings are shown in Table 4. Here again the Snellen, Ortho-Rater, and Sight-Screener are practically equivalent as to factor loadings for resolution. The loadings on the Telebinocular are much lower for both letter and circle targets. As would be expected, an accommodation factor appears to be

[*] Unpublished report, "Comparison Between Seven Tests of Depth Perception," Fort Eustis, Virginia.

TABLE 4

FACTOR LOADINGS OF NEAR VISION TESTS[*]

Instrument	Resolution	Accommodation	Form	Interference
Reduced Snellen	0.53 0.60	0.42 0.66	0.19 0.40	0.00 0.15
Ortho-Rater	0.54 0.70	0.57 0.70	0.02 0.14	0.16 0.37
Sight-Screener	0.59 0.69	0.39 0.53	0.01 0.17	0.00 0.23
Telebinocular (letters)	0.41 0.43	0.37 0.47	0.19 0.26	0.02 0.07
Telebinocular (circles)	0.38 0.56	0.39 0.50	0.03 0.18	0.02 0.26

[*] The Adjutant General's Office PRS Report No. 742, August, 1947, p. 54.

TABLE 5
FACTOR LOADINGS OF VERTICAL PHORIA TESTS*

Instrument		Vertical Phoria		Fusion		Specific	
Maddox rod	Far	0.43		−0.27		0.13	
	Near	0.20		−0.33		0.09	
Ortho-Rater	Far	0.50	0.73	−0.05	−0.12	0.22	
	Near	0.49	0.73	−0.04	0.05	0.71	0.76
Sight-Screener	Far	0.40	0.57	0.48	0.78	—	
	Near	0.47	0.54	0.57	0.62	—	
Telebinocular	Far	0.41	0.49	0.10	0.17	—	
	Near	—		—		—	

* The Adjutant General's Office PRS Report No. 742, p. 60.

present in all tests. The Ortho-Rater scores are affected slightly more by this factor as compared with the other devices. A form factor is present in both the Snellen and Telebinocular letters, which would be expected, but these two instruments present the lowest (practically zero) interference factors.

The factor loadings on the vertical phoria tests for distant and near vision on all devices are summarized in Table 5. Two factors, vertical phoria and so-called "fusion," are revealed in this analysis for all tests, while a specific instrument factor appears for the Ortho-Rater only, especially in the test at the near distance.

For the tests of far vertical phoria with the Maddox rod, Sight-Screener, and Telebinocular, the factor loadings for vertical phoria are relatively low and practically

equivalent. The Ortho-Rater test shows the highest factor loadings for vertical phoria. On the other hand, the Ortho-Rater shows the lowest factor loadings for "fusion" with the Telebinocular a close second. The variability of the Sight-Screener scores is greatly affected by this factor.

For the tests of vertical phoria at near vision, a large part of the variability of the Ortho-Rater scores is accounted for by a specific machine factor, peculiar to this instrument. This finding points to a definite area in which the Ortho-Rater might be improved. With the high loading already present on vertical phoria, elimination of the machine factor might greatly increase the efficiency of this instrument.

The Telebinocular does not have a test of near vertical phoria. As in the far vertical phoria test the Sight-Screener scores for

TABLE 6
FACTOR LOADINGS OF LATERAL PHORIA TESTS*

Instrument		Lateral Phoria		Fusion		Specific	
Maddox rod	Far	0.60		0.39		—	
	Near	0.58		0.41		—	
Ortho-Rater	Far	0.81	0.92	0.03	−0.10	0.09	0.17
	Near	0.65	0.68	0.06	0.09	0.05	0.11
Sight-Screener	Far	0.71	0.75	−0.04	−0.08	—	—
	Near	0.47	0.49	0.00	0.01	—	—
Telebinocular	Far	0.71	0.77	0.03	−0.04	—	—
	Near	0.57	0.70	0.02	−0.05	—	—

* The Adjutant General's Office PRS Report No. 742, August, 1947, p. 60.

near vertical phoria are greatly influenced by the "fusion" factor. The near Maddox-rod scores are affected, also, by this factor, and present the lowest factor loadings for near vertical phoria.

For the lateral phoria tests on all instruments, the factor loadings for both far and near vision are presented in Table 6.

For far lateral phoria loadings, the devices are ranked as follows: Ortho-Rater highest, 0.81 to 0.92; Sight-Screener and Telebinocular close second, 0.71 to 0.77; and Maddox rod third with 0.60. The Maddox rod is the only test affected significantly

SUMMARY

1. In general, the machine tests are as reliable, or are more reliable, than the corresponding clinical tests.

2. For monocular far acuity, the coefficients of reliability are practically the same for all tests. The coefficients range from 0.78 to 0.97.

3. For monocular near acuity, the consistency of the Ortho-Rater measures is slightly greater ($r = 0.80$ to 0.90) than for the other devices ($r = 0.71$ to 0.78).

4. For binocular acuity at both far and

TABLE 7
FACTOR LOADINGS OF DEPTH PERCEPTION TESTS*

Instrument	Depth		Form		Interference		Specific	
Ortho-Rater	0.61	0.69	0.04	0.11	−0.02	0.03	—	
Sight-Screener	0.43	0.44	0.03	0.11	0.03	0.06	0.31	0.38
Telebinocular	0.32	0.35	−0.13	−0.17	0.21	0.30	—	

* The Adjutant General's Office PRS Report No. 742, August, 1947, p. 54.

by the "fusion" factor, while the Ortho-Rater presents a slight loading on a specific instrument factor.

For near lateral phoria loadings, the Ortho-Rater again ranks the highest, 0.65 to 0.68, with the Telebinocular second, 0.57 to 0.70, Maddox rod third, 0.58, and the Sight-Screener the lowest, 0.47 to 0.49. Again the Maddox-rod scores are the only ones affected, significantly, by the "fusion" factor. There is a very slight machine factor affecting the Ortho-Rater scores.

The factor loadings of the tests of depth perception are presented in Table 7. The Ortho-Rater has the highest factor loading for depth, 0.61 to 0.69, while the Sight-Screener and Telebinocular have relatively low loadings on this factor, 0.43 to 0.44 and 0.32 to 0.35, respectively. The Sight-Screener scores are affected by a specific machine factor, while those of the Telebinocular are affected somewhat by both form and interference factors.

near distances, the reliability of the Ortho-Rater is the highest ($r = 0.80$ to 0.93) of the three machine tests.

5. The reliability of the clinical test of binocular acuity is equivalent to that of the Ortho-Rater for far vision ($r = 0.81$ to 0.97), but is lowest of all for near vision ($r = 0.67$).

6. For far vertical phoria, the Ortho-Rater is most consistent ($r = 0.79$), while the other three devices are equally less consistent ($r = 0.61$ to 0.64).

7. For near vertical phoria, the Ortho-Rater and clinical measures are equivalent in reliability ($r = 0.73$ and 0.74), while the Sight-Screener is much lower ($r = 0.55$).

8. Except for a slight advantage of the Ortho-Rater on far lateral phoria, all tests are equally consistent for both far and near lateral phoria.

9. The Ortho-Rater test of depth perception is the most reliable ($r = 0.83$), followed by the Telebinocular ($r = 0.79$),

Howard-Dolman ($r = 0.72$), and Sight-Screener ($r = 0.57$).

10. The validity coefficients of the tests of monocular acuity for both far and near vision are practically equivalent for the Ortho-Rater and Sight-Screener ($r = 0.71$ to 0.84), as compared with the Telebinocular ($r = 0.55$ to 0.58).

11. For binocular acuity, both far and near, the validity coefficients for the Ortho-Rater are the highest ($r = 0.90$ to 0.70), for the Sight-Screener next ($r = 0.71$ to 0.64), and for the Telebinocular lowest (near only) ($r = 0.55$).

12. For vertical phoria, both far and near, the validity coefficients are quite low for all devices ($r = 0.29$ to 0.50).

13. For far lateral phoria, the validity coefficients for the Ortho-Rater are much higher ($r = 0.57$ to 0.70), than for the other two devices ($r = 0.37$) each.

14. For near lateral phoria the validity coefficients of the Ortho-Rater and Telebinocular are practically equivalent ($r = 0.67$ to 0.68), while that for the Sight-Screener is somewhat lower ($r = 0.54$).

15. In the factor analysis of far visual acuity, the Sight-Screener and Ortho-Rater are equivalent to the Snellen chart on the factor of resolution; whereas, the Telebinocular loadings are lower on this factor. Significant form factors are revealed in the Snellen and Sight-Screener tests, while accommodation and interference factors affect the Telebinocular test and a specific machine factor affects the Ortho-Rater test.

16. For near vision, the factor loadings for resolution are lowest for the Telebinocular while for the other three devices the loadings are equivalent. A factor of accommodation affects all tests of near vision, but affects the Snellen and Ortho-Rater tests more than the others. A form factor is present in the Snellen and Telebinocular tests of near vision, while a specific machine factor is present in the Ortho-Rater test.

17. Although the Ortho-Rater shows the highest loading for vertical phoria for both far and near, it suffers from a specific instrument factor, especially at near. On the other hand, it reveals the lowest factor loading for "fusion."

18. The Ortho-Rater leads all instruments in factor loadings for lateral phoria, both far and near. All machine tests show higher factor loadings for lateral phoria than the Maddox Rod test. The latter is affected, also, by the "fusion" factor.

19. The Ortho-Rater presents the highest factor loadings for depth perception. The other two devices are affected by form, interference, or specific machine factors.

CONCLUSIONS

1. It is evident that a machine test of visual factors can be used to predict clinical factors with a fair degree of accuracy and consistency.

2. For visual acuity measures, the Ortho-Rater is slightly more reliable and valid than the other devices.

3. For vertical phoria, the Ortho-Rater is most consistent, but the validity coefficients for all devices are relatively low.

4. For far lateral phoria, the Ortho-Rater is slightly more consistent and is definitely more valid than the other devices.

5. In the measurement of far visual acuity, the Ortho-Rater and Sight-Screener are equivalent as to the factor of resolution, but all three instruments are adversely affected by one or more other factors.

6. All tests for near vision are affected by factors other than resolution.

7. The Ortho-Rater presents the highest factor loading for vertical phoria, but suffers from a specific machine factor.

8. The Ortho-Rater presents the highest factor loading for lateral phoria.

9. The Ortho-Rater presents the highest factor loading for depth perception and is least affected by other factors.

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STUDIES OF HUMAN TEARS*

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The first chemical analysis of tears was recorded in 1791 by Fourcroy and Van Quelin.[1] Subsequent analyses have been made.[2,3] The most recent one was that reported by Ridley and Brown, in 1930.[5e]

Fleming,[6] in 1922, demonstrated that tears had the property of lyzing certain saprophytic cocci. He showed that this was an enzyme-like substance which he named lysozyme. This substance has been found in nasal mucus, sputum, various tissue extracts, and egg white. The ready availability of egg white provided a convenient source of material. Therefore, chemical studies of lysozyme have dealt with this egg-white substance which is considered the typical lysozyme.[7] It has been shown to be a basic protein containing 16-percent nitrogen and 2- to 3-percent sulfur. It is of small molecular size and has a molecular weight of 14,000 to 17,000.[8]

Available evidence suggests that the "lysozyme" from various tissues and secretions of the body are essentially similar to egg-white lysozyme.[7e,9,10] Roberts and co-workers[7c] found that lysozymes of egg white and of cat's saliva were both basic and had similar solubility and sedimentation constants. However, the two agents were antigenically distinct.

Thompson[11] concluded from a review of the literature that lysozymes from various sources are similar in chemical constitution and properties, and that differences in chemical makeup sufficient to produce antigenic differentiation do not negate the essential identity of these enzymes. It should be understood that the egg-white lysozymes used in these above studies were not crystalline although of fairly high purity.

The present study was undertaken in an effort to analyze human tears further with particular interest in the fraction containing lysozyme activity.[†] For fractionation of plasma proteins several methods have been employed such as salt fractionation, ultracentrifugation, and electrophoresis.

Although salting-out methods have been useful, it has been stated that these fractions do not fulfill the criteria necessary to establish them as chemical individuals.[12] It has been suggested that many of the fractions isolated by this method might have been altered by the severity of the treatment used.[13] Ultracentrifuge or gravity methods of separation have been helpful but contributed only little toward the progress in isolation of components.

The moving boundary method of electrophoresis has been employed recently with considerable success.[14,15] This technique has proven of great importance especially for the estimation of the components of many proteins that at one time had been considered as being homogeneous. Tiselius emphasizes that electrophoresis is a very mild agent of separation and thus is likely to produce a constituent nearly unaltered from its natural state. However, the components found do not necessarily represent chemical individuals.

Previous analyses of proteins in the human tears have been based on salting-out procedures. Ridley and Brown, in 1930,[5e] determined the amount of protein soluble in 50-percent $(NH_4)_2SO_4$ which they called albumin. The remainder or insoluble protein was designated globulin.

Electrophoretic analyses of tears have not been recorded, although such analyses have been made on the vitreous humor and on ground-up lenses of cattle by Hesselvik,[16] and crystalline egg-white lysozyme has been

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† We employ the classic definition for lysozyme activity; that is, the lysis of *M. lysodeikticus.*

similarly analyzed by Alderton, Ward and Fevold.[8]

EXPERIMENTAL PROCEDURE

Tears were collected from the normal eyes of 215 volunteers (430 eyes). Sterile drawn-glass pipettes were used. Approximately 0.1 ml. were taken from each eye of every individual. Benzyl bromide was used frequently as a lacrimating agent. Earlier analysis of lysozyme activity showed that over 0.1 ml. of tears could be taken from an eye following benzyl bromide stimulation without a detectable reduction in lysozyme

TABLE 1
COMPOSITION OF NORMAL HUMAN TEARS

Fraction	Mg/1 ml.	Percentage
Original tears	18.7	100.0
Nondialyzable	9.1	48.6
NaCl	4.9	26.2
Dialyzable other than NaCl	4.7	25.1

content.[17] At different times, two batches of 14 ml. of tears and one of 13 ml. were obtained.

A. ANALYTICAL METHODS

1. *Total solids.* Total solids were found by placing 1 ml. of normal human tears in a weighing bottle and the water removed by evaporation at 105°C. It was then heated further for 1 hour at 105°C., cooled in a desiccator and weighed. The residue weighed 18.7 mg.

2. *Chloride content.* An amount, 2.288 mg., of the dried tears were removed from the bottle in which the total solid determination was made and the chloride content was determined gravimetrically. The yield was 16.0 percent of chloride or 26.6 percent of NaCl. Table 1 presents the results.

3. *Dialysis.* Tears were separated into dialyzable and nondialyzable fractions. Ten ml. of distilled water were added to 1.5 ml. of

clear tears. This solution was placed in cellophane tubing and dialyzed at 5°C. against 15 changes of 10-ml. volumes of distilled water. The dialysates were pooled. The final three dialysates gave negative tests for the chloride ion using silver nitrate. The dialysate and the nondialyzable material were dried from the frozen state. The yield of dialysate was 14 mg. or 55 percent; the yield of nondialyzable material was 11.5 mg. or 45 percent. A small amount of material adhered to the walls of the bottles which accounted for the slight loss, since 1.5 ml. of tears should have yielded 1.5×18.7 or 28 mg. and only $14.0 + 11.5$ or 25.6 mg. were recovered.

In another experiment 3.2 ml. of tears were dialyzed at 5°C. versus running distilled water for 24 hours. The solution was removed from the cellophane tubing and dried at 105°C.; this weighed 29.9 mg. representing 48.6 percent of nondialyzable material. This latter determination is probably more accurate than the first method (45 percent) since the method employed was more exact. Table 1 includes these data.

B. ELECTROPHORETIC ANALYSES

1. *Separation.* Fourteen ml. of these pooled normal human tears were centrifuged and filtered through paper in order to remove extraneous materials. The filtrate was then put into cellophane tubing and dialyzed for 72 hours against phosphate buffer, pH 7.9 and ionic strength 0.1. Electrophoretic analyses* were made in the usual manner.[14, 15] The current was 19 ma.; the potential gradient was 10.8 volts/cm. At a later date another sample of 14 ml. of pooled normal human tears was similarly studied and the same results obtained.

Four components were seen at pH 7.9. Three of these migrated toward the negative pole and were positively charged, the fourth component was negatively charged. Percentages and mobilities of each component were

* Apparatus manufactured by Klett Mfg. Co., New York.

determined. Chart 1 reproduces a diagrammatic representation of the descending side taken after 7,020 seconds, and Table 2 gives the results obtained. Component 1 was easily

DIAGRAMMATIC REPRODUCTION
TEARS 3-II-48 DESCENDING 7020 SECONDS
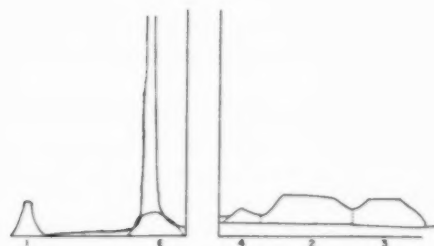
Chart 1 (Smolens, Leopold, and Parker). A diagrammatic representation of the descending side taken after 7,020 seconds.

isolated since it migrated in a direction opposite to that of Components 2, 3, and 4.

2. Lysozyme activity of components. In an effort to determine in which components the lysozyme activity resided, estimations were made of the ability of the pooled fresh tears, and of the components isolated electrophoretically to cause lysis of Micrococcus lysodeikticus. The method employed was that of Smolens and Charney.[38] Table 3 shows the results.

It was found that the original tears which had been dialyzed but not subjected to elec-

TABLE 2
RESULTS OF ELECTROPHORETIC ANALYSIS

Component	Percentage	Mobility ($u_d \times 10^6$ cm.^{2} volt^{-1} sec.$^{-1}$)
1	15.1	−9.8
2	42.8	11.6
3	34.4	18.0
4	7.2	6.7

trophoresis and the combined Components 2, 3, and 4 which had been isolated electrophoretically lyzed the substrate in a very high and equal dilution. Component 1 had no activity. No effort was made to separate Components 2, 3, and 4 as the amount of the tears available was two small. No conclusion can be made as to whether all of the activity is contained in any single electrophoretic component. The evidence shows that the lysozyme active portions lie in Components 2, 3, and 4. Not one of these fractions had the same mobility as that found for crystalline egg-white lysozyme by Alderton, Ward, and Fevold.[8] It appears, therefore, that tears lysozyme differs, by electrophoretic analysis, from crystallized egg-white lysozyme.

C. AMMONIUM SULFATE FRACTIONATION.

1. Separation. Ammonium sulfate fractionation was attempted on 11 ml. recovered from the electrophoresis cell. An equal vol-

TABLE 3
LYSOZYME ACTIVITY OF TEAR FRACTIONS

Fraction	Final Dilution of Fraction ×1,000												
	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1,024	1:2,048	1:4,096	1:8,192	1:16,380	1:32,760
Original tears	+*	+	+	+	+	+	+	+	+	±	0	0	0	
1 component	−	−	0	0	0	0	0	0	0	0	0	0	0	
2, 3, 4 components	+	+	+	+	+	+	+	+	+	±	0	0	0	
(NH₄)₂SO₄ ppt. pH 7.0	+	+	+	+	+	+	+	+	0	0	0	0	0	
(NH₄)₂SO₄ super. pH 7.0	+	+	+	+	+	+	+	+	+	±	0	0	0	
(NH₄)₂SO₄ ppt. pH 4.7	+	+	+	+	+	+	+	+	+	±	0	0	0	
(NH₄)₂SO₄ super. pH 4.7	+	+	+	+	+	+	+	+	+	±	0	0	0	
Lysozyme†	+	+	+	+	+	+	+	+	+	+	+	+	±	0

* + =Complete lysis.
± =Partial lysis.
0 =No lysis.
† Lysozyme =6 times recrystallized lysozyme from egg white.

ume of saturated ammonium sulfate was added. The pH of the mixture was 7.0. This was kept at 5°C. for 20 hours, centrifuged in the cold, and the supernate poured off. The sediment was washed twice with cold 50-percent ammonium sulfate and the two washings were combined with the supernate. Fifteen ml. of distilled water were used to dissolve the precipitate.

Both the supernate and the dissolved precipitate were put into cellophane tubing and dialyzed at 5°C. versus running distilled water until free of sulfate, phosphate, and chloride (about 54 hours). The yield for ammonium sulfate precipitate was 14.7 percent and the supernate yield was 85.3 percent.

Fifty-eight mg. of this were taken up in 7.5 ml. of 0.85-percent NaCl. This dissolved readily with very slight opalescence. $(NH_4)_2SO_4$ was added to 50-percent concentration. Since there was no buffer present, the pH of the mixture was 4.7. This was allowed to stand for three hours at 5°C. and centrifuged. The same procedure, as described above, was repeated. The yield of the precipitate was 41.0 percent and of the supernate 59 percent. There was a striking difference between the separation effected at the two pH levels. Repetition of the procedure gave almost identical results. At pH 7.0, the precipitate yield was 13.7 percent and the supernate 86.3 percent, and at pH 4.7, 41 percent and 59 percent, respectively.

From the salting-out procedure pH 4.7, the soluble fraction equals 59 percent. This agrees closely with the finding of Ridley and Brown.[50] In their report they designated the soluble portion albumin as constituting 58.5 percent of the total. However, salt fractionation at pH 7.0 produced a markedly different result which resembled more closely those found by electrophoresis.

2. *Nitrogen and phosphorus contents.* Nitrogen determinations were made using the micro-Dumas method. Results were: Original undialized tears equal 7.1 percent; $(NH_4)_2SO_4$ supernate, pH 7.0, equals 13

percent and $(NH_4)_2SO_4$ precipitate equals 11.5 percent.

Phosphorus determinations were made on each of the two fractions using the method of King.[19] Negative results were obtained. From the result obtained in the positive P control it may be concluded that with the amount of sample used that less than 0.5 percent P is contained in the nondialyzable fraction of tears. This means that very little, if any, phospho- or nucleo-proteins are present in tears.

3. *Molisch reaction.* Tears which had been dialyzed gave a positive Molisch reaction indicating the presence of sugar. The 50 percent $(NH_4)_2SO_4$ supernate at pH 7.0 gave a very faint test using 2 mg. per ml.; whereas, the precipitate gave a much stronger reaction with a solution of 1 mg. per ml.

4. *Lysozyme activity.* Estimations were made of the ability of the ammonium sulfate fractions obtained at pH 7.0 and 4.7, to cause the lysis of M. lysodeikticus. The same method mentioned previously was employed.[17] It was found that, at pH 4.7, there was equal activity, but, at pH 7.0, the $(NH_4)_2SO_4$ precipitate contained only 25 percent of the activity of the supernate. Results are shown in Table 3.

5. *Ultraviolet absorption spectra.* None of the amino acids and only a few special proteins absorb light in the visible region. However, nearly all of the proteins and certain of the amino acids exhibit a strong specific absorption between 3,000 and 2,500 Angstrom units, in the ultraviolet region. The property of proteins to absorb ultraviolet light is most likely due to their content of aromatic amino acids, phenylalanine, tyrosine, and tryptophan. It is commonly accepted that the aromatic hydrocarbons are the only ones which exhibit band spectra. The ability of other amino acids to absorb light is slight in comparison to that of the aromatic amino acids.[20]

Ultraviolet absorption spectra were determined on pooled human tears and the results are shown in Chart 2. Maximum ab-

sorption occurred at 2,775 Angstrom units. The same figure obtained for the supernate isolated by 50-percent ammonium sulfate fractionation at pH 7.9 (Charts 2 and 3). This is most likely due to the tryptophan and or tyrosine content since the maxima for these amino acids are about 2,800 Angstrom units.[21]

Similar results have been obtained not only from the usual proteins but from virus and bacterial proteins.[22a-c]

demonstrates a specific antigenic dissimilarity.

DISCUSSION

The results show that the nondialyzable material in tears can be separated into at least four components by electrophoretic technique. The three components that migrated to the negative pole at pH 7.9 possessed all of the lysozyme activity. The mobilities of these components differed from those ascribed to crystalline egg-white lyso-

U.V. ABSORPTION OF NORMAL HUMAN TEARS
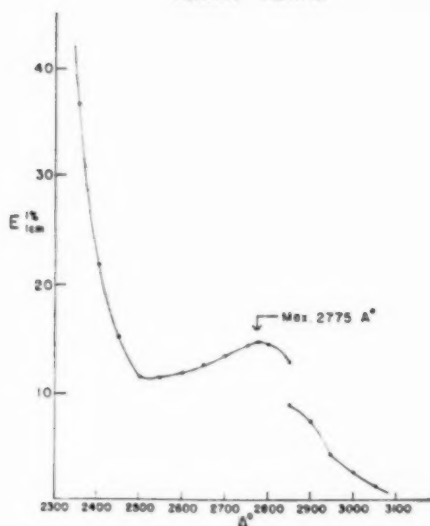
Chart 2 (Smolens, Leopold, and Parker). Ultraviolet absorption spectra were determined on pooled human tears.

U.V. ABSORPTION OF pH7 50% (NH₄)₂SO₄ SUPERNATE
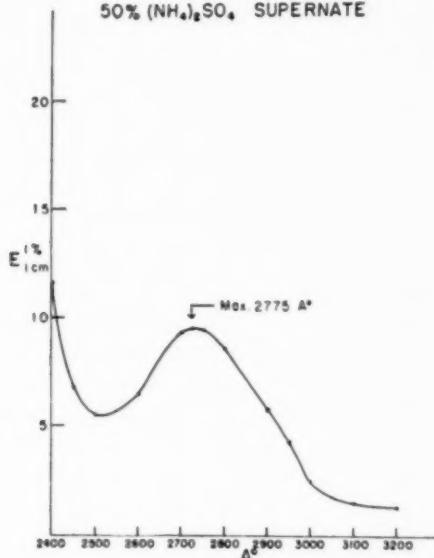
Chart 3 (Smolens, Leopold, and Parker). Ultraviolet absorption spectra were determined on pooled human tears.

D. INFLUENCE OF EGG-WHITE LYSOZYME ANTISERA

In order to demonstrate an antigenic difference of crystalline egg-white lysozyme and of tear lysozyme, the ability of each to lyze M. lysodeikticus, in the presence of rabbit antisera prepared versus crystalline egg-white lysozyme, was ascertained. It is evident from results shown in Table 4 that the antisera inhibits only the homologous and not the heterologous lysozyme which

zyme. Further, specific antisera prepared against crystalline egg-white lysozyme failed to inhibit the lytic activity of tears. These differences clearly demonstrate immunologic and chemical differences between egg-white and tear lysozymes. As has been shown previously,[18] this again points out that the ability of any material to lyze M. lysodeikticus is probably not to be ascribed to any specific entity.

It is also evident that the three compo-

nents have mobilities and isoelectric points that have not been described as occurring in human sera. This may mean that these substances are not present in human sera and that they are produced in the tear glands, or that these components exist in human sera in very low concentrations. It should be hibit characteristic electrophoretic mobilities which are completely different from the tear components.

Electrophoretic analysis of calf thymus histone has been reported by Weissman and Graf[23] to give a value of $u_d = ^+9.1$. Bloom, and others[24] have found a fraction B, an-

TABLE 4

INHIBITION EXPERIMENT DEMONSTRATING SPECIFICITY DIFFERENCE OF CRYSTALLINE
EGG-WHITE LYSOZYME AND TEAR FRACTION

Dilution	Time of Reading Hrs.	ml. Antiserum per Tube							
		0.1	0.05	0.025	0.0125	0.006	0.003	0.0015	0
1:80×10² Egg white lysozyme	1½	+	+	+	+	+	+	+	+
	2½	+	+	+	+	+	+	+	+
	4	+	+	+	+	+	+	+	+
1:800×10³	1½	0	0	0	+	+	+	+	+
	2½	0	0	0	+	+	+	+	+
	4	0	0	0	+	+	+	+	+
1:8000×10³	1½	0	0	0	0	0	0	0	0
	2½	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
1:80×10³ (NH₄)₂SO₄ pH 7.0 Supernate of tears	1½	+	+	+	+	+	+	+	+
	2½	+	+	+	+	+	+	+	+
	4	+	+	+	+	+	+	+	+
1:800×10²	1½	±	±	±	±	±	±	±	0
	2½	±	±	±	±	±	±	±	±
	4	±	±	±	±	±	±	±	±
1:8000×10³	1½	0	0	0	0	0	0	0	0
	2½	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
Control (no lysozyme)	1½	0	0	0	0	0	0	0	0
	2½	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0

+ = complete lysis (no inhibition).
± = partial lysis.
0 = no lysis (inhibition).
Note: Overnight readings showed that all of the tubes containing more than 0.003 ml. serum gave a ± reading. This was due to the lytic action of the serum.

possible to decide this by the use of immunologic methods. Since the lysozyme concentration of the tears is decreased with lacrimation, it is possible that the source of lysozyme resides in the bacterial flora normally present in the eye.

Ridley and Brown[5e] have designated their (NH₄)₂SO₄ fractions as albumin and globulin following the classic nomenclature. These terms are untenable in view of the mobilities reported here. Albumins and globulins ex-

thracis that has a $u_d = ^+8.0$ Both of these analyses were carried out at pH 5.5. These mobilities, which represent highly basic substances, are slower than those reported here for tear components. The discrepancy should be even more apparent if the difference in pH is taken into consideration. To date we have been unable to find in the literature any substance with similar electrophoretic mobility as those found in the tears.

It is of interest to note the difference in re-

sults obtained by 50 percent $(NH_4)_2SO_4$ fractionation at pH 4.7 and 7.0. Quantitatively our data at pH 4.7 closely corroborate the findings reported by Ridley and Brown.[5e]

The salting out at pH 7.0 seems to produce fractions similar to those obtained electrophoretically, if yields and lytic activities are used as criteria. The decrease of precipitate with rise in pH suggests the presence of an acidic fraction. Seibert found analogous phenomena in her analysis of tuberculin preparations. She discovered that this can be contributed to contamination with nucleic acid and a polysaccharide.[25] The negative result obtained for P would rule out the presence of nucleic acid in any appreciable quantity in tears.

The positive Molisch test on the nondialyzable fraction indicates the presence of a sugar. It is interesting that both the dialyzed tears and the 50-percent $(NH_4)_2SO_4$ pH 7.0 precipitate give much stronger Molisch reactions than the supernate. This latter trace reaction may be due to contamination with small amounts of precipitate.

The possibility of an acidic polysaccharide is strengthened indirectly by the N values. A very high N content would be expected in tear fractions because of their basic isoelectric points. Contrary to this expectation low-N figures were given. If this were a simple protein a value of 16-percent N should be expected. However, the fraction found in tears contained only 12-to 13-percent N. This fraction must be either lacking or very low in N content as well as being acidic. Further experiments should clarify this point.

SUMMARY

1. Tears contain at least four components by electrophoretic analyses. One migrated to the positive pole and three to the negative pole.

2. Lysozyme activity resides in the three components that migrate to the negative pole.

3. Chemical and immunologic differences are demonstrated between tear components and crystalline egg-white lysozyme.

4. Ammonium sulfate fractionation of tears yielded two components in varying concentration depending on the pH at which the fractionation was performed.

5. The total solids in tears was 1.87 percent.

6. The chloride content of tears was 16-percent chloride or 26.2-percent sodium chloride.

7. Ultraviolet absorption showed a typical protein curve denoting the presence of aromatic amino acids.

8. The tears were divided into dialyzable and nondialyzable fractions. The yield of dialysate was 51.4 percent and the nondialyzable was 48.6 percent.

9. A positive Molisch reaction indicates the presence of a sugar.

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DISCUSSION

DR. DAVID G. COGAN (Boston, Massachusetts): Dr. Leopold's subject is on normal human tears, but I think it would be very interesting to know if he has made any determination of lysozyme concentration of tears under pathologic conditions.

DR. TRYGVE GUNDERSEN (Boston, Massachusetts): It may be of interest at this time to draw attention to an apparent error in Duke-Elder's *Textbook of Ophthalmology*, v. 1, p. 639. In Table XXXII—Composition of Tears (in grams percent) Ridley-Brown (1930) are quoted as finding tear sugar 0.65.

Dr. John Talbot and I, in an analysis of approximately 10 tear samples, found this figure about 10 times too high. The error is apparently one of a decimal point.

DR. LEOPOLD (closing): We have run lysozyme concentrations on normal and on pathologic tears. We have not done any chemical or electrophoretic analyses on pathologic tears because of the large amounts required. In order to get an analysis of one particular condition, you would have to get a great number of eyes; you must have at least 11 milliliters in order to run one electrophoretic analysis on our apparatus. For example, if one planned to investigate superficial punctate keratitis, one would have to get at least one tenth of a milliliter per eye. One hundred and ten eyes would be required in order to get enough for that analysis.

However, we have run lysozyme concentrations on superficial punctate keratitis and the resulting impression is that they are high in lysozyme content. At first Dr. Meyer in New York, who is also interested in this problem, believed that he was obtaining high values in the superficial punctate, but I believe when he used the new method of chemical analysis which does not depend on lysis of the Micrococcus lysodeikticus itself, he did not feel that the lysozme content was elevated in these eyes.

We have not reported the sugar content on total tears, but believe Dr. Gundersen is correct.

EFFECT OF BAL (2, 3 DIMERCAPTOPROPANOL) ON INTRAOCULAR COPPER*

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BAL (2, 3 dimercaptopropanol) was developed early in the war by Peters, Stocken, Thompson,[1] and their associates as an agent to counteract the effects of arsenical war gases, particularly Lewisite (B-chlorovinyl-dichloroarsine). Subsequently its systemic effect as an antidote in heavy metal poisoning was described, and there have been reports concerning this action in mercury,[2] lead,[3] gold,[4] and arsenic[5] reactions. The antidotal effect is ascribed to the reaction of BAL with the heavy metal to form a stable, relatively nontoxic ring compound, in which the metal is not available for combination with the tissues and inactivation of sulfhydryl containing enzyme systems. Additionally there are indications that BAL may remove the heavy metal from the enzyme system even after combination.

This study was directed toward the possible detoxification of intraocular copper with BAL systemic administration of the intravenous salt which, according to McCance and Widdowson,[6] causes a 20-fold increase in urinary excretion of copper. The severe chemical inflammation caused by intraocular copper has been known since the classical experiments of Leber[7] but the mechanisms are still poorly understood. Our studies concerning the effects of copper on the eye will be the subject of another paper and we shall largely concern ourselves here with studies with BAL.

Chemically, copper and BAL react quantitatively to form a heavy, bluish-green precipitate which settles rapidly out of solution. The precipitate is insoluble in alcohol, ether, hot and cold water, and concentrated hydro-chloric acid. It is soluble in concentrated nitric acid with the liberation of hydrogen. On the basis of analogy with the reaction of BAL with mercury chloride, the copper compound formed probably has the structural formula:
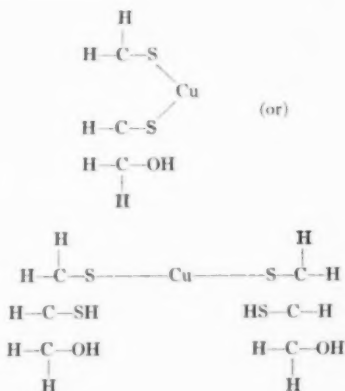
The reaction, as should be anticipated, occurs only with ionic copper and it was not possible to coat copper particles with BAL as metallic copper is insoluble in BAL solutions.

Experimental procedures

Male albino rabbits weighing 5 to 6 pounds were used throughout the study. Anesthesia was obtained with 10-percent sodium pentobarbital intravenously and 0.5-percent pontocaine topically.

Foreign material was placed in the anterior chamber with a Troncoso[8] introducer inserted through a small keratome incision at the limbus superiorly. Eserine was usually instilled in the conjunctival sac 30 minutes preoperatively to prevent iris prolapse.

Material was placed in the vitreous by

means of a specially constructed 14-gauge needle introduced into the eye through the pars plana superiorly. After the needle was in the eye and under direct observation through the pupil, the cooper or other material was forced into the vitreous with an obturator and the needle was withdrawn. There was a moderate loss of vitreous with this procedure but the eyes were white and apparently normal externally within 24 hours.

Injections of BAL into the anterior chamber were made with a 27-gauge needle introduced obliquely through the cornea to prevent loss of the injected material. Usually 0.15 cc. of aqueous was removed and a similar volume of fluid introduced through the same needle, care being taken not to touch the iris with the needle or entirely collapse the anterior chamber. BAL was injected into the vitreous through a 27-gauge needle inserted into the vitreous through the pars plana.

EFFECT OF BAL COPPER

Equimolar concentrations of BAL* and copper sulfate were mixed and the resulting precipitate filtered and repeatedly washed with distilled water. Immediately prior to use it was washed with alcohol and ether to sterilize and then introduced into either the anterior chamber or vitreous.

The precipitate was slowly absorbed from the anterior chamber and after a period of 60 to 90 days disappeared entirely without residue. Initially, a slight ciliary injection occurred and persisted for about 24 hours. It was attributed to the operative manipulation. At no time following this was there any evidence of inflammation provided the precipitate did not occlude the pupil. In the latter instance, a severe inflammatory reaction with secondary glaucoma ensued, an effect attributed to mechanical occlusion of the pupil. When the pupil was not occluded,

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* The pure BAL used in this study was kindly furnished by Hynson, Westcott, and Dunning, Baltimore, Maryland.

the precipitate caused a minimal reaction and disappeared at a rate that varied directly with the amount injected.

Histologic study of these eyes showed but slight evidence of inflammatory reaction. The cornea, lens, and posterior segment were free of the precipitate which was scattered through the iris and ciliary body. The angle contained some rather large particles but was open. The iris showed the most marked deposit of the copper salt in the area in contact and there was some endothelial proliferation here. Other copper was deep in the stroma with some round-cell infiltration but the inflammatory reaction was practically absent (fig. 1).

The precipitate was well tolerated by the vitreous and did not produce an inflammation if it did not come in contact with the retina. It remained glistening in the vitreous for periods as long as 60 days without change in appearance, size, or position.

Histologic study of these eyes indicated that in most the injection was through the anterior retina rather than the pars plana. The copper salt caused no cellular reaction and the retina in bulk and section showed no abnormality (fig. 2).

OCULAR TOLERANCE TO BAL

Studies were directed toward the determination of ocular tolerance to BAL when applied topically and when injected into either the vitreous or anterior chamber. Hughes,[9] Mann, Pirie, and Pullinger,[10] and Leopold and Adler[11] accurately determined the tolerance when topically applied in a variety of animals including man. Our findings did not vary from these investigators except that we found that BAL in the Fuqua base of Hughes was irritating on repeated application. Concentrations of BAL up to 20 percent in either aqueous or ointment bases were well tolerated by the cornea.

Leopold and Steele[12] showed that a therapeutic concentration of BAL following topical application penetrated the cornea. Their work was not repeated because the formation
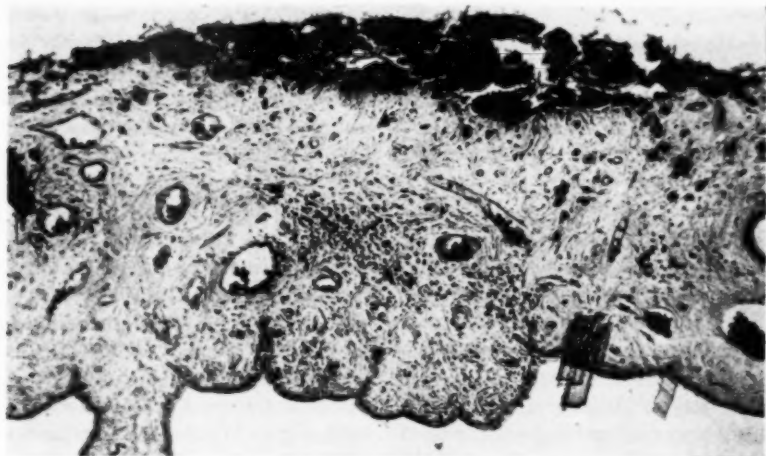
Fig. 1 (Newell, Cooper, and Farmer). Salt of BAL and copper sulfate scattered through the iris after 40 days. The inflammatory reaction is minimal.

of the precipitate of BAL-copper in the anterior chamber was evidence of the penetration through the cornea of BAL in eyes containing copper.

Considerable difficulty was experienced in finding a solution of BAL which could be injected into the anterior chamber without reaction. The solubility in water of various lots of BAL varied considerably and the toxicity varied from lot to lot. Injections of 1-percent BAL (by volume) caused a severe iritis with corneal infiltration and vascularization with permanent corneal scarring. Injection of 0.125-percent BAL in water was well tolerated provided the solution was freshly prepared and the operative manipulation was minimal.

EFFECT OF BAL ON COPPER IN THE ANTERIOR CHAMBER

Copper in the anterior chamber caused a remarkably constant reaction. Within 24 hours the foreign body was covered with leukocytes, the iris was diffusely injected, and there was an outpouring of fibrin into the anterior chamber. The acute phase lasted 7 to 8 days and subsided with the iris in-

Fig. 2 (Newell, Cooper, and Farmer). Salt of BAL and copper sulfate in vitreous 74 days after introduction. The retina is normal except at the wound of entrance of the needle used for introducing the salt.

jected only in the sector containing the foreign body. Approximately 4 to 5 days after introduction of the copper, a massive vascularization into the substantia propria commenced in the meridian nearest the foreign body and extended to a point just beyond the foreign body. At this time the leukocytic covering of the copper diminished and the foreign body became more metallic in appearance, although it was not visible.

Recession of the blood vessels began one month after maximal corneal involvement and, with their retrogression, copper was deposited in the cornea in the area involved in the vascularization. The copper particle was adherent to the cornea and iris and remained there for months without any reaction in the iris. These eyes remained unchanged for months except that the copper particle became more and more superficial. No animal completely extruded the copper but it was a simple procedure to dissect it from the cornea.

Slitlamp examination showed the metallic area to be composed of highly refractile crystals in either the endothelium or Descemet's membrane. The metallic area was present only where there had been vascularization, although the blood vessels appeared to be superficial to the coppering. In some animals a crescentic area in Bowman's membrane developed, separated by a clear interval from the main mass deep in the cornea; the mechanism of this deposition is not clear but seems to be related to the distribution of new blood vessels in the cornea.

Ten-percent BAL in aquaphor ointment was applied topically 4 times daily to eyes with copper in the anterior chamber. The initial application was made 4 hours after insertion of the metal in the eye. The right eye only was treated; the left eye, with copper in a similar location, was used as a control.

The severity of the polymorphic cellular reaction to copper was definitely lessened by topical BAL as long as the therapy was maintained. Reaction followed, however, within 24 hours after therapy was discontinued but was less severe than in the control eye. The aqueous showed a bluish coloration surrounding the foreign body within 4 hours after treatment was begun; this was attributed to the formation of the bluish salt of BAL-copper.

The most outstanding reaction of topical application of BAL was the severe corneal damage occurring in eyes with copper in the anterior chamber. After 2 or 3 installations of the BAL ointment the cornea was cloudy and diffusely edematous with numerous punctate staining areas. Slitlamp examination showed marked edema of the epithelium with multiple abrasions and cellular infiltration of the substantia propria. Frequently the cornea was so cloudy that the iris and pupil could be seen only with difficulty. Initially it was thought that this reaction was due only to the BAL, but topical application of the same ointment to normal eyes was well tolerated.

Leopold[12] indicated that corneas injured with Lewisite were more sensitive to the toxic effects of BAL than the normal cornea. Continued application of BAL to eyes containing copper resulted eventually in perforation of the globe. Interruption of the treatment within 72 hours resulted in rapid corneal healing with minute scars in the substantia propria.

Intramuscular administration of 2.5 mg./kilogram of 10-percent BAL in peanut oil to animals with copper in the anterior chamber delayed the leukocytic reaction. To maintain therapeutic blood levels, the drug had to be injected every 4 hours and, as soon as the therapy was discontinued, the typical effects of copper followed.

Injection of 0.125-percent BAL into the anterior chamber of eyes containing copper resulted in a diminution of the leukocytic reaction plus the usual blue color. Interest-

ingly, there was no corneal reaction as occurred with topical application of the drug. Again, the administration of BAL had to be continued to prevent the copper reactions which occurred as soon as the drug was stopped.

EFFECT OF BAL ON COPPER IN THE VITREOUS

The reaction of the eye to copper in the vitreous varied considerably but in general two basic reactions were found to occur. A fibrous tissue proliferation with organization of the vitreous was most typical, the severity proportional to the rate of oxidation (and hence the surface) of the copper and the distance of the copper from the retina. Thus, a small enough piece of copper located as far as possible from the retina did not cause any gross reaction. The characteristic chalcosis oculi, with bluish-green discoloration of the iris and vitreous followed by deterioration of the eye, occurred only in the presence of blood in the vitreous. Study is being directed toward the possibility of a different copper salt being formed in the presence of hemorrhage.

BAL administered topically and intramuscularly understandably had no effect on copper in the vitreous. Intravitreal injection of 0.125-percent BAL may have had a minimal effect on preventing the fibrous tissue reaction of copper. It was difficult, however, to evaluate accurately the result, since a small piece of copper aroused such a minimal reaction immediately that no treatment was indicated, while a large piece or pieces of copper resulted in severe fibrosis of the vitreous which intravitreal BAL did not effect. Experiments were not done on eyes containing both blood and copper because of the long period of development of chalcosis oculi.

DISCUSSION

There have been several attempts to eliminate the toxic effects of copper in the eye,

most of them more ingenious than practical. Removal of the offending substance is, of course, indicated whenever possible and there have been numerous cases reported of complete recession of all of the ocular effects of copper once the exciting particle was removed.

Fragments in the posterior segment, however, frequently cannot be removed without destroying the eye. For copper in this location, some investigators have attempted to coat the particle with a metal, such as gold, well tolerated by the eye, while others have attempted to create a ferrous alloy which could then be removed with a magnet. Meller[13] reported a beneficial action of topically applied sodium thiosulfate which reacts with copper to form an insoluble salt well tolerated by the eye.

This study has indicated the possibility of detoxifying intraocular copper by some dithio compound that must, however, have certain chemical and physical characteristics not possessed by BAL. Since it is necessary to administer the drug over long periods, it must be nontoxic, be effective with oral administration, and have a molecule of such size or structure that it passes into the eye from the blood stream. Preferably it should be highly disassociated so it may be administered by iontophoresis, and it should form a salt with copper which is not toxic to the eye and of small enough size to be passed into the systemic circulation and be excreted.

CONCLUSIONS

1. BAL and copper react quantitatively to form a salt which is well tolerated when injected into either the anterior chamber or vitreous.

2. Topical application of BAL to eyes containing copper in the anterior chamber diminished the inflammatory effect of copper but caused severe corneal damage, the mechanism of which is not understood. BAL injected into the anterior chamber did not

cause corneal damage but had to be repeated at frequent intervals to be effective.

3. The effect of BAL on copper in the vitreous was minimal regardless of the mode of administration.

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DISCUSSION

DR. JAMES RICHARDSON (Chicago, Illinois): I would like to ask if intracorneal injections of the BAL copper-sulfate precipitate were used?

DR. JONAS S. FRIEDENWALD (Baltimore, Maryland): I am very much intrigued by the idea that has been suggested that some copper-binding substance could be taken orally over long periods to prevent the toxic concentration of copper ions in the eye. There are such substances.

The thio-ureas form very insoluble copper salts and some of the symptoms of chronic thio-urea poisoning exhibit the characteristic pattern of copper deficiency. We need a certain amount of copper for survival. Animals that are copper-deficient lose their hair pigmentation and become ill, and so forth, and Dr. Richter, who has studied the effects of chronic thio-urea poisoning, has found that the characteristic symptoms of that poisoning are similar to that of copper deficiency.

Even if one had a copper remover that acted orally, it would be a total copper remover and might produce harm elsewhere.

Dr. Newell (closing): The precipitate of BAL and copper sulfate was not injected into the cornea. Parenthetically, copper in the cornea causes a severe reaction with marked infiltration within 24 hours and within the week the cornea is necrotic and the foreign body is extruded.

Dr. Friedenwald's suggestion of using the thio-ureas in detoxifying copper reminds me that Meller in 1938 used sodium thiosulfate orally, topically, and subconjunctivally to create an insoluble copper salt well tolerated by the animal eye. Clinically, however, his work was not borne out.

THE MOVEMENT OF MONOSACCHARIDES INTO AND OUT OF THE AQUEOUS HUMOR*

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Two theories of the mechanism of aqueous formation are currently debated. One school of thought supports the view that the aqueous is largely a dialysate which is modified to a certain extent by the metabolism of intraocular tissues and possibly by some secretory activity. The proponents of this theory hold that the main osmotic constituents of the aqueous, that is, sodium salts, enter the aqueous humor via a simple diffusion augmented by a slight hydrostatic force.[1] The other school of thought supports the view that the aqueous is largely a secretion.[2, 3] This theory, therefore, proposes that the main osmotic constituents are secreted into the aqueous.

Interpretation of the observed fact that glucose and urea exist in relative deficit in the aqueous humor as compared with plasma water has been the source of dispute between the protagonists of these two views. Those who feel that the aqueous is largely a dialysate contend that this deviation from a true equilibrium can be explained on the basis of a utilization of glucose by tissues bathed by the aqueous and/or an alteration of this dialysate by some secondary membrane in the system. A possible secretion of these substances into and/or out of the aqueous may occur at this membrane.

On the other hand, those who feel that the aqueous is largely a secretion hold that the deficiency of glucose and urea can be accounted for by the osmotic work done on the system by the secretion of sodium salts. Under this view, urea and glucose may enter by simple diffusion, although the possibility of secretion of these substances is not excluded. Therefore, independent observations of the exact means by which glucose and urea enter and leave the aqueous, that is, by secretion or diffusion, and of the extent by which metabolic activity modifies the concentrations, will be of material value in a definition of the dynamic factors involved in aqueous formation.

This information cannot be obtained from a knowledge of the distribution of these compounds between the aqueous and plasma at the steady state.[†] Steady-state ratios only indicate whether work is required for their maintenance but do not permit conclusions

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† The term "steady state" is preferred to "equilibrium" since the latter may be confused with "thermodynamic equilibrium." A thermodynamic equilibrium requires that the concentrations of the nonelectrolytes be the same in both aqueous and plasma water. A steady state, as applied to a dynamic system, denotes a system in which there is no change with time and in which the concentration ratio may be any value.

as to the mechanism involved. Moreover, one cannot generally conclude from studies of the rate of passage of a substance across an unaltered barrier whether this substance is being secreted or is passing by simple diffusion. However, glucose is unique in this respect; work with other animal membranes has indicated that from a comparison of the rates of movement of various monosaccharides one can determine whether glucose is being secreted by the barrier.

It has been shown that glucose and galactose move across the intestinal wall approximately 7 to 10 times faster than the pentoses, xylose and arabinose.[4] Similar differentials have been observed in the kidney tubule.[5] This preferential movement of the hexoses is probably due to secretion.[6] On the other hand, the rate of absorption of the hexoses from the peritoneal cavity is substantially the same as that of the pentoses; that is, the movement seems to be by simple diffusion across a capillary membrane.[7]

One may assume, therefore, that glucose and galactose are secreted by the membrane in question if their movement is strikingly more rapid than that of the pentoses. If the rates of penetration of hexoses and pentoses are substantially the same, the process may be considered to be a simple diffusion. The work here reported was undertaken to determine which of these alternatives applies in the movement of these substances into the aqueous humor.

If the utilization of a sugar by ocular tissues is the sole factor responsible for its aqueous deficit, the pentoses should be equally distributed between plasma and aqueous water at a steady state, since it is quite certain that ocular tissues do not utilize pentoses to any appreciable extent. Thus, a comparison of the steady-state ratios of pentoses and glucose should provide a test of the theory that the deficit of glucose is due to its utilization by intraocular tissues. Moreover, if the monosaccharides are neither secreted into nor out of the aqueous, the process responsible for any deviation of the pentose

steady-state ratios from unity might reasonably be assumed to alter the glucose ratio in the same direction.

Many reports have been published on the movement of various carbohydrates into the aqueous. Robertson and Williams[8] showed that following the injection of glucose, its concentration in the aqueous increases; but the aqueous-plasma ratios they determined never exceeded 50 percent. Kinsey and Grant[9] reported a similar movement of fructose, with a steady-state ratio of about 50 percent. Weld, Feindel, and Davson[10] studied the accumulation of xylose, glucose, sucrose, and raffinose (a trisaccharide) in the aqueous and concluded that molecular weight is the determining factor in the movement; however, no steady-state ratios were determined. On the other hand, Rosner and Bellows[11] reached the conclusion that sorbitol accumulates in the aqueous humor much more slowly than glucose, although the molecular weights and structures of the two are similar. Again no steady-state ratio was obtained.

CALCULATIONS

To compare quantitatively the rates of movement of two or more substances across a membrane, some coefficient relating the concentrations of the substances in aqueous and plasma to the rate of movement must be calculated. A mathematical expression of this relationship is given by the following fundamental equation.

$$(1) \qquad \frac{dC_a}{dT} = k_1 C_p - k_2 C_a$$

where C_a = Concentration of substance in aqueous.
C_p = Concentration of substance in plasma.
k_1 = Coefficient of transfer from plasma to aqueous.
k_2 = Coefficient of transfer from aqueous to plasma.

At the steady state:

$$k_1 C_p = k_2 C_a$$

Let

$$\alpha = \frac{C_a}{C_p} = \text{steady state ratio}$$

Then

$$(2) \qquad k_2 = \frac{k_1}{\alpha}$$

Thus

$$(3) \qquad \frac{dC_a}{dT} = k_1 \left(C_p - \frac{C_a}{\alpha} \right)$$

No commitments are made concerning the force driving the solute in either direction. The conclusion concerning this must be drawn from a comparison of k_1 and k_2 values of the various sugars.

If the concentration in the plasma remains constant, expression (3) can be integrated within limits of T_1 and T_2 and rearranged to:

$$(4) \qquad k_1 = \frac{\alpha}{T_2 - T_1} \ln \left[\frac{\alpha C_p - C_{a1}}{\alpha C_p - C_{a2}} \right]$$

A slightly different expression is obtained if C_p is not constant but still varies as a straight-line function of time. In this case $C_p = u + v T$ where u and v are constants that must be determined graphically from each experiment. Substituting:

$$\frac{dC_a}{dT} = k_1 \left(u + vT - \frac{C_a}{\alpha} \right)$$

This equation has the general solution:

$$(5) \qquad C_a = \alpha u + \alpha v T - \frac{\alpha^2 v}{k_1} + c e^{-k_1 T/\alpha}$$

where c is a constant of integration. Equation (5) has no exact solution for k_1 but, by using the values of u and v for each particular experiment and the aqueous levels determined at T_1 and T_2, a sufficiently accurate figure for k_1 can be obtained by means of Newton's approximation.

k_2 is calculated from expression (2).

k_1 and k_2 incorporate the ratio of the area of the blood-aqueous barrier to the volume of the aqueous. This ratio is assumed to be reasonably constant from animal to animal.

As noted by Palm,[12] consideration should also be given to the assumption that the diffusing substance distributes itself immediately and in equal concentration throughout the aqueous. Actually, a concentration gradient may be established in the aqueous fluid. In the presence of such a gradient, k_1 calculated from aqueous levels determined at 10 and 30 minutes would be lower than that

calculated from data obtained at 5 and 25 minutes. Only the values for 1-arabinose indicated with an asterisk in Table 3 were determined over the later time period. They are the lowest obtained for this particular sugar and suggest that a concentration gradient may be established within the aqueous fluid.

METHODS

Albino rabbits, lightly anesthetized with nembutal, were used in this study. Sedation was considered necessary since struggling and excitement of the animal during a critical stage raises the blood sugar and vitiates
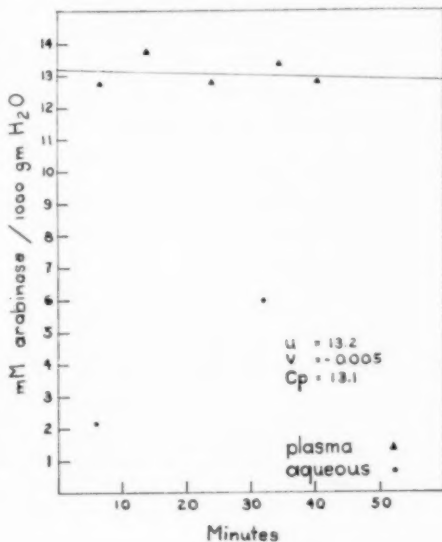
Fig. 1 (Harris and Gehrsitz). Sample data of one experiment from which the coefficients of transfer were calculated. The points represent the determined blood and aqueous levels. u and v are the constants determined graphically for this particular experiment, u being the ordinate intercept and v being the slope of the plasma concentration-time curve. C_p is the average plasma value and is used in the first approximation calculation of k_1 from Equation 4.

the results. The sugars, d-glucose, d-galactose, d-xylose, 1-arabinose, and d-arabinose, were used. Each animal was given a subcutaneous injection followed by an intrave-

nous injection. The intravenous dose was 1 to 1.5 cc. per kilo of a 15-percent solution of the pentoses or an 18-percent solution of the hexoses. Five times this amount was given subcutaneously. By such a combination of injections, the plasma level of the sugar could be maintained as a straight-line function of time during the period of observation. Sample data from one experiment are graphically represented in figure 1.

Using heparin as an anticoagulant, periodic blood samples were taken from the

ous revealed that these filtrates contained no nonsugar reducing substances. Thus, the values reported are true sugar values. To determine absolute values for galactose and the pentoses, yeast fermentation was used on filtrates of these sugars.

Determination of the steady-state ratio of the various sugars presents a problem, since it is difficult, if not impossible, to maintain a constant level in the blood plasma for the hours necessary to achieve a steady state. Reformed aqueous is said to recover its glu-
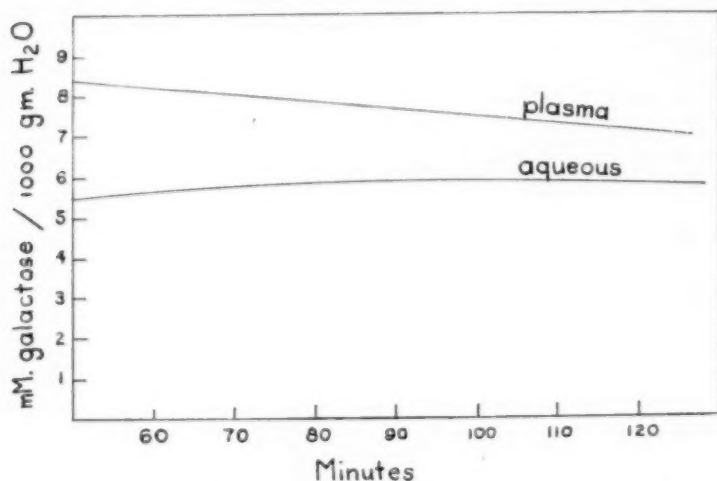
Fig. 2 (Harris and Gehrsitz). Graphic representation of the approach to the steady state of sugars diffusing into the aqueous where the plasma level is falling slowly. The curves mirror the trend of many experiments. In practice, the steady-state level was calculated by averaging determinations made at the inflection point.

marginal ear vein for analysis of the plasma sugar content. The value thus obtained was found to agree with that of arterial blood taken by heart puncture. A heart puncture was done at the end of each experiment for sugar and water determination. The first aqueous sample was generally taken 2 to 5 minutes after the intravenous injection; the second, 10 to 20 minutes later.

All sugars were determined by using the new reagent of Somogyi[15] on barium hydroxide-zinc sulfate filtrates. Yeast fermentation of sample filtrates of blood and aque-

cose level quite quickly.[14] In our hands, however, this did not prove a reliable method of determining the steady-state level. The ratio of the glucose content of the reformed aqueous to that of the plasma was found to vary inconsistently with that of the initial aqueous, even though periods as long as $1\frac{1}{2}$ hours had elapsed. In every case, the ratio was higher in the reformed than in the initial aqueous.

Examination of equation (1) shows that a steady state must be reached when $\frac{dC_a}{dT} = 0$.

The ratio of the blood level to the aqueous level at that point is the true steady-state ratio. Since the plasma sugar level cannot be maintained, the best alternative is to determine the peak or inflection point of the aqueous concentration during a period when the blood level is falling as a straight-line function of time. The ratio of the blood to the aqueous level at that point is the true steady state for the constituent in question.

Figure 2 shows an ideal graph of this relationship. It does not represent experimental data. A curve similar to this cannot be plotted for any one experiment because only two estimations of the aqueous concentration can be obtained. Moreover, the exact slope of the blood level cannot be duplicated in any two animals, or even in the same animal. Thus, the peak in aqueous concentration is not likely to occur at the same point on the time scale in any two experiments. For this reason, a composite curve of many animals cannot be constructed.

The average of a series of aqueous-plasma ratios determined at or near the peak was found to provide a reasonably exact approximation of the steady-state ratio. Experimentally, the peak for all sugars was demonstrated to be reached in about 85 to 105 minutes. The two aqueous samples were drawn 10 minutes apart during this time interval. The peak was considered to be reached if the aqueous levels did not vary more than 0.5 mM/kilo of water. Prior to the series, this figure was arbitrarily established from a consideration of the technical errors and the shape of the curve.

The time course of the plasma sugar level was determined for each experiment, starting 10 minutes before and extending through 10 minutes after the aqueous samples were withdrawn. If the plasma analyses would not fit a straight line, the experiment was discarded.

In actual practice, little difficulty was encountered in meeting these standards with xylose, arabinose, and galactose. Since the blood concentration of glucose had to be raised to a much higher level than that of the other sugars, the technical error contributed much more to the absolute difference. Nevertheless, the glucose steady state was determined in this same manner as a test of the validity of the assumptions and to insure experimental uniformity.

RESULTS

The steady-state values for the four sugars are given in Table 1 and are summarized in Table 2. The data indicate that the peak in aqueous concentration was approximated since the aqueous levels either fell or rose slightly or remained the same during the period of observation. The ratios for all sugars are below 1.0.

The values for k_1, the coefficient of transfer from plasma to aqueous, are given in Table 3. There is little difference between the rates of entrance of pentoses and hexoses. A closer parallel might be expected between d-xylose and l- and d-arabinose than was obtained. This difference may be due to the errors introduced by the assumptions made in the calculation of k_1. However, it may also be due to some restrictive influence at the barrier. Such a possibility was indicated by the work of Rosner and Bellows[11] on sorbitol.

The values for k_2, the coefficient of transfer out, are given in Table 4. Here again, no significant difference is shown between the movement of hexoses and pentoses.

DISCUSSION

In the introduction it was pointed out that where glucose and galactose are secreted across a membrane, their k values are 7 to 10 times greater than such values obtained when movement is by simple diffusion. The results show that the k_1 values for the hexoses and pentoses studied are essentially the same; consequently, glucose is not secreted into the aqueous. A similar evaluation of k_2 values indicates that glucose is not secreted out of the aqueous. It is concluded, therefore, that

TABLE 1

STEADY-STATE RATIOS

d-Glucose

Animal No.	Time—Minutes Sample 1	Time—Minutes Sample 2	Conc. in aqueous mM/1,000 gm. H_2O Sample 1	Conc. in aqueous mM/1,000 gm. H_2O Sample 2	$\dfrac{C_a}{C_p}$
496	81:30	91:30	13.3	13.1	0.76 / 0.78
494	85:15	95:15	9.6	9.6	0.91 / 0.91
488	85:15	96:00	18.3	18.3	0.86 / 0.90
483	86:30	96:30	14.0	14.4	0.77 / 0.81
490	90:00	100:00	11.0	11.0	0.85 / 0.88
492	90:00	100:15	13.8	14.7	0.76 / 0.86

d-Galactose

Animal No.	Time—Minutes Sample 1	Time—Minutes Sample 2	Conc. in aqueous mM/1,000 gm. H_2O Sample 1	Conc. in aqueous mM/1,000 gm. H_2O Sample 2	$\dfrac{C_a}{C_p}$
475	75:00	90:00	6.5	6.4	0.69 / 0.75
487	81:00	90:30	5.2	4.9	0.77 / 0.77
481	90:45	106:15	6.1	5.9	0.71 / 0.76
483	95:15	105:45	4.6	4.8	0.71 / 0.76
498	95:15	105:45	6.9	6.7	0.82 / 0.83
499	95:15	106:00	6.5	6.4	0.63 / 0.64
488	100:30	111:45	4.7	5.1	0.77 / 0.88

d-Xylose

Animal No.	Time—Minutes Sample 1	Time—Minutes Sample 2	Conc. in aqueous mM/1,000 gm. H_2O Sample 1	Conc. in aqueous mM/1,000 gm. H_2O Sample 2	$\dfrac{C_a}{C_p}$
492	84:45	95:15	4.7	4.9	0.78 / 0.85
482	85:15	95:30	4.3	4.1	0.76 / 0.80
481	85:15	96:15	5.2	5.0	0.73 / 0.77
491	85.30	95:45	5.8	5.5	0.87 / 0.89
497	85:45	96:00	5.6	5.5	0.74 / 0.78
490	95:15	105:15	5.3	4.8	0.85 / 0.81

l-Arabinose

Animal No.	Time—Minutes Sample 1	Time—Minutes Sample 2	Conc. in aqueous mM/1,000 gm. H_2O Sample 1	Conc. in aqueous mM/1,000 gm. H_2O Sample 2	$\dfrac{C_a}{C_p}$
493	*85:15	95:00	6.1	6.3	0.68 / 0.75
484	85:15	95:30	4.7	4.5	0.73 / 0.75
487	85:15	97:45	6.9	7.0	0.67 / 0.73
490	85:45	96:15	7.2	7.1	0.74 / 0.81
483	86:30	96:30	4.7	5.0	0.65 / 0.75
489	90:30	101:30	5.2	5.1	0.64 / 0.69

d-Arabinose

Animal No.	Time—Minutes Sample 1	Time—Minutes Sample 2	Conc. in aqueous mM/1,000 gm. H_2O Sample 1	Conc. in aqueous mM/1,000 gm. H_2O Sample 2	$\dfrac{C_a}{C_p}$
490	85:00	95:00	5.6	6.1	0.52 / 0.58
486	85:00	95:15	3.7	4.1	0.47 / 0.56
489	85:30	96:00	5.2	5.1	0.57 / 0.58
487	85:45	95:45	4.5	4.5	0.49 / 0.52

glucose enters and leaves the aqueous by a process of diffusion, not secretion.

As stated previously, if the metabolism of sugars were the only cause of deficit in the aqueous, the steady-state ratio of the pentoses would be expected to be one, and that of glucose below one. All sugars studied reach a steady-state ratio significantly below 1.0. This proves conclusively that the glucose deficit normally found is not due solely to its utilization by the lens and retina.* Indeed, it is surprising that the steady-state value for glucose is higher than that of other sugars. Since glucose is utilized by intraocular tissues, a lower value would reasonably be expected, all other things be-

TABLE 2

SUMMARY OF MEAN STEADY-STATE RATIOS

Sugar	Number of Animals	Mean	Standard Deviation
d-Glucose	6	0.84	±0.06
d-Galactose	7	0.75	±0.08
d-Xylose	6	0.80	±0.05
l-Arabinose	6	0.72	±0.04
d-Arabinose	4	0.54	

Two possibilities remain whereby a substance such as glucose, which is secreted neither into nor out of the aqueous, may exist in a relative deficit not accounted for by metabolic utilization. The first is that sufficient energy may be applied by the hydrostatic pressure in the capillaries to account

TABLE 3

COEFFICIENT OF TRANSFER (k_1) FROM PLASMA TO AQUEOUS

d-Glucose	d-Galactose	d-Xylose	l-Arabinose	d-Arabinose
2.9×10^{-2}	4.2×10^{-2}	4.5×10^{-2}	2.1×10^{-2}	2.3×10^{-2}
2.9	3.1	4.3	2.0	1.7
2.1	2.9	4.2	2.0	1.5
2.0	2.5	3.8	1.8	1.0
1.9	2.4	3.0	1.6	
1.6	2.1	2.7	1.5	
1.4		1.8	*1.3	
		1.5	*0.9	
Mean 2.1×10^{-2}	2.9×10^{-2}	3.2×10^{-2}	1.7×10^{-2}	1.6×10^{-2}
S.D. $\pm 0.6 \times 10^{-2}$	$\pm 0.7 \times 10^{-2}$	$\pm 1.2 \times 10^{-2}$	$\pm 0.4 \times 10^{-2}$	

* Time interval between intravenous injection and first aqueous sample—11 and 13 minutes, respectively

ing equal. The high glucose steady-state value may be due to the fact that the blood and aqueous concentrations of this substance must be raised higher than other sugars to determine the steady-state ratio by the method employed.

* Since completion of our studies we have received a copy of a recent paper by Davson and Duke-Elder[18] who reported studies similar in some respects to our own. These authors found little difference in the rate of uptake of glucose, xylose, galactose, and 3-methyl-glucose in the cat. Our data conforms to this. Good agreement is shown between their steady-state value for glucose in the rabbit and that reported here. However, these authors did not measure the steady-state ratio for other sugars. From their studies, they concluded that the relative deficit of glucose can be explained on the basis of metabolic removal by the lens and retina. This view is incompatible with our findings in the rabbit.

for the deficit. This possibility was considered by Duke-Elder and Davson[16] and by Friedenwald,[3] but was found to be incompatible with the known pressure gradients.

The other possibility, suggested by Kinsey and Grant,[2] is that sufficient osmotic work can be done by some normal constituent of the aqueous to account for this deficit of

TABLE 4

COEFFICIENT OF TRANSFER (k_2) FROM AQUEOUS TO PLASMA

Sugar	k_2
d-Glucose	2.5×10^{-2}
d-Galactose	3.9×10^{-2}
d-Xylose	4.0×10^{-2}
l-Arabinose	2.4×10^{-2}
d-Arabinose	2.9×10^{-2}

nonelectrolytes. These authors envisage a through and through flow of aqueous driven by a secretion of sodium, the flow resulting from the osmotic influence of the secreted salts. The glucose deficit at the steady state is considered to be due to the relatively low rate of diffusion of this substance into the aqueous stream. Or, as Friedenwald[3] phrased it, "the least work toward establishing that steady state would occur if fluid relatively hypotonic in nonelectrolytes were transported." However, the secretion of sodium is not a necessary feature of this scheme if other means of doing osmotic work can be found.

If the aqueous humor is taken as the system, then the secretion of some substance into the aqueous involves work done on the system, and the deficit of nonelectrolytes results from work done by the system. If the system conforms to the second law of thermodynamics, then the work done on the system in the secretion of the substance must be equal to or exceed that done by the system in the formation of a glucose deficient fluid.* The work done on or by the system can be calculated from the equation:

$$w = nRT \ln \frac{C_1}{C_2}.$$

Calculations using this equation show that the work done by the system in the formation of a liter of aqueous with a glucose concentration of 80 mg. percent and an aqueous-plasma ratio of 0.8 is approximately 0.6 calories. A urea deficit, at physiologic concentrations, requires approximately one half this amount of work.

In a similar manner, the work done on the system in the secretion of a substance can be calculated if its concentration in aqueous and plasma is known.

Since the sodium analyses reported in the

literature do not show a consistent deviation from the Donnan equilibrium, that is, a true thermodynamic equilibrium, it is not possible to calculate the work theoretically done in its secretion, assuming for these purposes that it is secreted. However, using 1.0 calories as the minimum work that must be done, calculations indicate that the concentration of sodium chloride in the aqueous would be 1 mM/kilo of water in excess of a Donnan equilibrium if this substance were to satisfy the work requirements. This difference is too slight to be detected with regularity by the chemical methods that have been employed. Therefore, the possibility that a secretion of sodium may account for the glucose and urea deficit can be neither dismissed nor affirmed. Since there is no conclusive proof that sodium is secreted into the aqueous, it is advisable to evaluate other possible sources for osmotic work.

There is good evidence that ascorbic acid is secreted into the aqueous.[17] The work done on the system in the formation of a liter of aqueous with an ascorbic-acid concentration of 20 mg. percent and an aqueous-plasma ratio of 20 is calculated to be 2.0 calories. Therefore, the work necessary for the formation of a glucose deficient fluid is amply provided by the secretion of ascorbic acid into the aqueous, assuming all other substances enter by simple diffusion. Likewise, sufficient work is available to account for a urea deficit.

The fact that the work requirements are met in the rabbit if ascorbic acid is the sole substance secreted into the aqueous is not proof that the mechanism postulated is actually operating. There are other considerations.

First, since the concentration of ascorbic acid is not sufficient to account for the reported hyperosmotic pressure of the aqueous over plasma, other sources of osmotic work should be sought. For example, the formation of lactic acid from glucose by intraocular tissues, since it results in an increased osmotic activity, may aid in the

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* Since the work done on the system results in an increase in free energy of the system and the work done by the system results in a decrease, the work values will be opposite in sign. However, for our purpose, a comparison of the numerical values themselves is sufficient.

elaboration of an aqueous with a glucose and urea deficit in the manner suggested for ascorbic acid.

Second, although the low glucose and urea steady-state ratios have been the most consistently reported, osmotic work might reasonably be done on other aqueous constituents, for example, sodium salts. Yet, if the same amount of osmotic work that is performed on glucose was applied to the dilution of sodium salts, the resultant deviation from a true equilibrium would lie within the limits of error of the analytical methods that have been used.*

Finally, a thermodynamic balance which indicates that the secretion of ascorbic acid, perhaps supplemented by lactic-acid production, meets the necessary work requirements is only the first step in the proof that aqueous formation can be explained on this basis.

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* Within the limits of the work available, the steady-state ratio of a substance must also be influenced by its rate of diffusion into the aqueous. Thus, a substance which enters rapidly, such as ethyl alcohol,[12] would reasonably show the high steady-state ratio that has been reported, that is, approaching unity.

SUMMARY

A measure of the coefficient of transfer of d-glucose, d-galactose, d-xylose, l-arabinose, and d-arabinose into and out of the aqueous humor has been made in the rabbit. These coefficients have been shown to be substantially the same for the pentoses and hexoses. This indicates that glucose is neither secreted into nor out of the aqueous humor of the rabbit.

The steady-state ratios of all sugars studied was found to be substantially lower than 1.0 in the rabbit. The relative deficit of glucose in the aqueous of the rabbit cannot be accounted for solely on the basis of metabolic depletion.

The data obtained, using the rabbit, can be explained if ascorbic acid is considered to be the sole substance secreted into the aqueous. The production of lactic acid by intraocular tissues may be an additional source of osmotic work. The possibility of a secretion of sodium salts is not precluded.

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DISCUSSION

DR. V. EVERETT KINSEY (Boston, Massachusetts): I would like to point out, as I did to Dr. Harris last night, that I do not feel that it is possible to conclude whether glucose is secreted or diffused from the kind of data he obtained, although I do agree with his conclusion that it is diffused. I will try to point out in the following paper the additional kind of data which are necessary before conclusions can be drawn as to whether a substance enters the anterior chamber by secretion or diffusion.

DR. JONAS S. FRIEDENWALD (Baltimore, Maryland): As I follow Dr. Harris's argument, it seems to me he assumes there is no intraocular utilization of glucose. I would like to ask him whether that is true. If there were intraocular utilization of glucose, then more glucose would have to go in than his equations account for, and the disparity between the glucose transport and the pentose transport would have to appear.

DR. HARRIS (closing): Dr. Kinsey's objection, as he voiced it to me last night, is to our original premise that a comparison of the rates of transfer of various monosaccharides gives a basis for concluding whether glucose is secreted across some blood-aqueous barrier. The basis for this premise is included in the text of the paper. Across certain animal membranes, notably the intestine, the rate of transfer of glucose and galactose is much greater than that of the pentoses. This differential is eliminated by such metabolic poisons as sodium fluoride and phlorizin, indicating that the preferential

movement of glucose is due to some metabolic function of the membrane. Phosphorylation of glucose appears to be an essential part of this active transfer.

On the other hand, where the movement is by strict diffusion, as in solution or across a simple membrane such as the peritoneum, the hexoses and pentoses move at substantially the same rate, the pentoses having a slightly greater diffusion constant. It seems reasonable to conclude, therefore, that the movement is by diffusion if the rates of entrance are similar. Certainly, the burden of proof would rest with him who would interpret the data differently.

In answer to Dr. Friedenwald's question, we have not meant to infer that there is no intraocular utilization of glucose. Our kinetic results would be influenced by the intraocular metabolism of glucose if the rate of metabolism is proportional to the concentration in the aqueous. They would not mirror any intraocular utilization if it is constant and, thus, independent of the concentration in the ranges employed.

Since the latter is more likely, it is not surprising that our kinetic results do not demonstrate consumption of glucose by intraocular tissues. Parenthetically, it should be noted that the same considerations apply to a secretion at a blood-aqueous barrier.

One might expect the steady-state ratios to be demonstrably lower for glucose than for substances which are metabolically inert, such as xylose. This was not found and there are several possible explanations. One

important factor may be the concentrations employed in the experimental procedures. Glucose concentrations were maintained at a higher level than those of the other sugars.

Then, too, it may be that the metabolic activity of the intraocular tissues does not alter the concentration of glucose in the aqueous that one obtains for analysis by corneal puncture in the rabbit.

In this connection, the data presented in a recent paper by Davson and Duke-Elder are interesting. Studying the glucose distribution in the aphakic and normal eye of the cat and rabbit, they reported that, in the cat, the aqueous-glucose concentration was invariably higher in the aphakic than in the

normal eye. On the other hand, in the rabbit, the glucose concentration was consistently the same or lower in the aqueous of the aphakic eye than in the normal eye.

The diffusion of glucose across the iris must certainly be considered a possibility. All that we can reasonably say is that, as we measured it by withdrawing fluid from the anterior chamber, we found no evidence that the deficit of glucose normally present in the aqueous of the rabbit can be explained on the basis of intraocular utilization. It may well be that there is a species difference between the cat and rabbit which extends beyond the ability to concentrate ascorbic acid.

THE RATE OF FLOW OF AQUEOUS HUMOR*

I. The rate of disappearance of para-aminohippuric acid, radioactive Rayopake, and radioactive Diodrast from the aqueous humor of rabbits

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The present papers will be concerned with methods for measuring the rate of flow of aqueous and the physiologic implication of flow. The time relations governing the entrance and exit of substances in the aqueous and the distribution ratios of substances between aqueous and blood are significantly affected by the rate of flow and cannot be understood without due regard to it (Kinsey and Grant[1]).

Since the eye is a physical system where the intraocular pressure is determined by the

balance between the production and removal of aqueous, a knowledge of flow, and especially of its dependence on intraocular pressure, is of prime importance for an understanding of normal and abnormal intraocular pressure.

Finally, it is possible that the flow of aqueous in itself is of importance for the lens, since convection currents are probably more efficient than diffusion in moving material up to and away from the surface of the lens (Bárány[2]).

Determinations of the rate of aqueous flow using cannulation of the anterior chamber during the period of measurement cannot give physiologic values. Measurements aimed at establishing the rate of flow in eyes not altered by the procedures employed have to be done with indirect methods, by deriva-

tion from the time-concentration curve of a
test substance in the aqueous.

This seems to have been attempted for the
first time by Abe and Komura[3] who used
fluorescein as a test substance and carried
out the experiments on atropinized rabbits'
eyes. The value they obtained shows a sys-
tematic error because of inadequate mathe-
matical treatment.

Kinsey and Grant[1] derived the rate of
flow of aqueous for the rabbit from curves
representing the rate of accumulation of
various substances in the aqueous. In these
studies data from several animals were
pooled and certain assumptions regarding
the mode of entrance of the substances were
made; for example, electrolytes were as-
sumed to enter by secretion and not to be
able to pass the blood-aqueous barrier by
diffusion; nonelectrolytes were assumed to
diffuse through the blood-aqueous barrier.

While their data were generally consist-
ent with these assumptions, an independent
redetermination of the rate of flow is indi-
cated. The purpose of the present study is
to make such a determination and to draw
certain inferences from the flow rate thus
obtained, regarding the mode of entrance of
such physiologically important ions as so-
dium and chloride.

For convenience in presentation, the ma-
terial has been divided into two parts. The
first, the present paper, will be concerned
with the rate of disappearance from the
aqueous and the steady-state distribution
ratio aqueous to plasma of several substances
of graded molecular weight. The second will
deal with the use of these data in computing
the rate of flow of aqueous and the in-
ferences regarding the mode of entrance of
substances of physiologic importance.

METHODS

The rate of disappearance of a test sub-
stance from the anterior chamber would of
itself constitute a measure of the rate of flow
of aqueous, provided that (1) the substance
was not replaced from the blood, (2) it

could leave the anterior chamber only by
flow, and (3) it left the filtering angle at the
same rate as other constituents of the
aqueous humor. Under these conditions,
when a certain fraction of the aqueous
is removed from the anterior chamber
by flow per unit of time, the same fraction
of the total amount of test substance would
disappear. While it is not practical to fulfill
all of these ideal conditions, an experiment
can be set up in which the deviations are
slight. The experiments were designed in
such a way as to provide such conditions.

The deviations from the ideal experimen-
tal arrangement are imposed primarily by
the necessity of getting the substance into
the eye under physiologic conditions. The
most physiologic way to introduce the sub-
stance is by means of the blood stream. This
leads to difficulties, however, since the object
of the study is to determine the rate of dis-
appearance from the aqueous of the sub-
stance under conditions of essentially no re-
placement from the blood. It is desirable to
arrange the experiment so that once the sub-
stance is brought into the blood stream, and
from there into the aqueous, it is rapidly
removed from the blood again.

In the present study, this was accom-
plished by giving the test substance intra-
venously and selecting as test substances or-
ganic compounds which are actively excreted
by the kidneys at maximal rate.

The ultimate goal of having the blood
stream practically free of the substance
while there still was a measurable amount in
the aqueous was not reached, but the blood
concentrations during the test period were
so low that a small mathematical correction
based on knowledge of the steady-state dis-
tribution ratios (aqueous concentration/-
plasma concentration) of the observed values
was sufficient to take account of the presence
of test substance in the blood.

The requirement that the substance leave
the aqueous primarily by flow but still not
be held back preferentially at the filtering
angle was met by selecting materials of in-

termediate molecular weight. All of the desirable properties were encompassed in the following three substances: (1) para-aminohippuric acid (molecular weight, 194); (2) Rayopake, 2 Methyl-4-6 diketo-5-iodotetrahydropyridone-N-acetic acid (m.w., 308); and (3) Diodrast, 3, 5 diiodo-4-pyridone-N-acetic acid (m.w., 405).

The excretion of para-aminohippuric acid and Diodrast by the kidney approaches the theoretical maximum of total clearance of the blood by a single passage at low blood concentrations (Smith and others[4]). Rayopake is also rapidly excreted by the kidney. All three compounds have low toxicity and are only slightly adsorbed by the plasma proteins.

According to Hecht[5] the iodine compounds are unlikely to undergo any change in the body. Para-aminohippuric acid can be conjugated presumably by the liver, but it is extremely unlikely that this occurs also in the eye. While para-aminohippuric acid is readily estimated chemically, the current chemical methods for iodine are not accurate enough to determine the small amounts of the organic iodine compounds encountered in the experimental conditions here described.

In the experiments concerned with the rate of disappearance of the test substances, the aqueous samples contain only about one-millionth of the amount of substance administered to the animal. Accordingly, Diodrast and Rayopake were synthesized using radioactive iodine, and the compounds were determined by measuring the radioactivity present.

Unanesthetized male albino rabbits, weighing between 1.6 and 2.6 kg., were used in all the experiments. They were kept on a stock diet and given water at pleasure. No effort was made to increase their kidney blood flow by forcing fluids. At least 10 days were allowed to elapse between repeated paracenteses in the same animal; such eyes were checked with the slitlamp. Animals whose eyes showed hyperemic iris, synech-

ias, aqueous flare, or other signs of inflammation were discarded. Small lens opacities caused by accidental injury to the lens at previous punctures were tolerated, however. A large proportion of the animals injected with each substance had never been used before. No difference in behavior between the eyes of these animals and eyes thought to be completely recovered from previous punctures was detected.

In the experiments in which the rate of disappearance of para-aminohippuric acid was to be determined, an isotonic solution of the sodium salt was injected intravenously. The dose was 0.75 to 1.5 gm. and the time for injection was 5 to 7 minutes. No acute toxic effects, except a slight drowsiness, were observed in the rabbits.

In those experiments with the same substance in which the ratio of the concentration in the aqueous to that in the plasma under steady-state conditions was to be determined in intact animals, an intravenous injection immediately followed by an intraperitoneal one was given at the start, and intraperitoneal injections were repeated at 20-minute intervals for 3 to 4 hours.

In three instances steady-state ratios were determined over a period of 7 to 8 hours in animals whose kidneys had been tied off under nembutal anesthesia the evening before. The animals were awake before injection of para-aminohippuric acid. In these animals, too, repeated intraperitoneal injections were needed to keep up the plasma level of the test compound.

The rate of disappearance of the iodine compounds Rayopake and Diodrast was measured approximately 120 minutes after intravenous injection of 0.25 to 0.5 millicurie of radioactivity. The latter was contained in about 0.5 gm. of substance, which was dissolved in 10 ml. of water. The solution was adjusted to pH 7.0.

The steady-state values were all obtained in animals with ligated kidneys, operated the evening before under a short-acting barbiturate, alurate. About 0.1 millicurie was given

intravenously immediately after the operation, and next day when the animals were awake and still little affected by the nephrectomy, the aqueous and blood samples were taken. At this time the activity in the plasma was found to be declining slowly so that the results could be used for steady-state distribution ratios with small correction.

Micropipettes previously described by Kinsey[6] were used for removing aqueous. The first aqueous and first blood samples were taken about 2 hours after intravenous injection of the substance; the second aqueous and second blood samples were taken 1 hour later. Since the pontocaine which was used as a topical anesthetic produced a color with the reagents used in the determination of para-aminohippuric acid, these eyes were thoroughly rinsed and blotted before withdrawing aqueous. Blood was taken by heart puncture in heparinized syringes.

Para-aminohippuric acid was determined by the method outlined by Smith and others,[4] which consists of deproteinating in alkaline solution, and diazotization followed by colorimetry. This method was followed exactly except that the quantities of reagents used in carrying out analyses in aqueous humor were reduced proportionately to give the maximum color in the minimum volume (1.5 ml.) which could be read in the colorimeter used. The color produced is stable and Beer's law is obeyed up to concentrations of 5 mg. percent. Replicates of samples containing 1.5 mg. percent of p-aminohippuric acid agreed within ±1 percent. Control samples of aqueous humor and plasma gave no color when tested.

The two organic iodine compounds, Rayopake and Diodrast, were synthesized from their organic precursors and radioactive I^{131}. The substances were determined by measuring the radioactivity in dried samples of aqueous humor and whole plasma by means of a thin-wall beta counter and the usual planchent technique. Correction for self-absorption in the plasma samples was not necessary, since only ratios between

samples of the same kind are used in the calculations.

Tonometry calibrated for rabbits' eyes was performed in some experiments to determine whether the injection of the large volume of fluid containing the p-aminohippuric acid had any effect on intraocular pressure. The intraocular pressures did not differ significantly from normal. The reproducibility of the method is described elsewhere (Bárány[7]).

MATHEMATICAL TREATMENT

The experiments provide information about the concentration of the test substance in the aqueous humor and also in the plasma at two different times after injection. The object of the mathematical treatment is to derive the rate of disappearance as it would have been if the plasma concentration had been zero during the whole test period. Should this have been the case it can be safely assumed that the aqueous concentration would be expressed by a simple exponential function. In this instance the relation between the concentration in two aqueous samples interspaced by the time interval t_1 is given by:

$$(1) \qquad \frac{C_{Aq_2}}{C_{Aq_1}} = e^{-k_{out} \cdot t_1}$$

where C_{Aq_1} and C_{Aq_2} are the aqueous concentration at the beginning and end of the interval t_1, and k_{out} is the rate of disappearance. When time is measured in minutes, k_{out} is of the order of magnitude of 0.01. It is perhaps more convenient to speak of the half-life of the substance in the aqueous $t_{1/2}$, which is $0.693/k_{out}$.

The exponential relation (1) results from a differential equation which indicates that the rate of change of concentration is proportional to the concentration present in the aqueous, the volume being constant. The equation is:

$$\frac{dC_{Aq}}{dt} = -k_{out} \cdot C_{Aq}$$

When there is some of the substance cir-

culating in the plasma, the equation should contain a term indicating the possibility of entrance of substance from the blood stream. Assuming that the rate of entrance is proportional to the concentration in the plasma, for which experimental evidence will be given later in this paper, the differential equation becomes:

$$(2) \qquad \frac{dC_{Aq}}{dt} = k_{in} \cdot C_{pl} - k_{out} \cdot C_{Aq}$$

where k_{in} is the rate constant for entrance, and C_{pl} the plasma concentration.

After the first hour following injection, the plasma concentration was found to fall along a nearly exponential curve. This is described by:

$$(3) \qquad C_{pl} = C_{pl_0} \cdot e^{-k_{pl} \cdot t}$$

where C_{pl_1} and C_{pl} are the initial and momentary plasma concentrations, respectively, and k_{pl} is a rate constant for disappearance of the substance from the plasma. By inserting this expression in Equation (2) and solving the differential equation, the following expression is arrived at for the ratio of the concentration in the second aqueous sample to that of the first:

$$(4) \qquad \frac{C_{Aq_2}}{C_{Aq_1}} = e^{-k_{out} \cdot t_1} \left(1 + k_1 \cdot \frac{C_{pl_1}}{C_{Aq_1}} \cdot \frac{1 - e^{-(k_{pl} - k_{out}) t_1}}{k_{pl} - k_{out}} \right)$$

When the second term in the large parenthesis is zero, Equation (4) degenerates into Equation (1). The large parenthesis thus represents the effect of the presence of the test substance in the blood.

In expression (4), t_1, C_{Aq_1}, C_{Aq_2}, and C_{pl_1} are given directly by the experiment. K_{pl} is derived from t_1 and the two plasma concentrations by means of Equation (3). This leaves both k_{in} and k_{out} unknown so that it is necessary to obtain supplementary data to solve for either. It will be shown that data can be obtained by finding a value for the ratio k_{in}/k_{out} in independent experiments. That this ratio is identical with the steady-state ratio of the concentration in the aqueous to that in the plasma can be seen from

the following. At steady state, there is no change in aqueous concentration. Hence Equation (2) becomes:

$$0 = k_{in} \cdot C_{pl \text{ at. state}} - k_{out} \cdot C_{Aq \text{ st. state.}}$$

It follows that:

$$k_{in} = k_{out} \cdot \frac{C_{Aq \text{ st. state}}}{C_{pl \text{ at. state}}} = k_{out} \cdot R$$

where R is the steady-state distribution ratio aqueous/plasma.

To solve k_{out} in (4), k_{in} is expressed as $k_{out} \cdot R$, and a mean value of R, obtained from a separate series of experiments, is used. The solution of k_{out} is then arrived at by successive approximations. In solving the equation much time is saved by preparing graphs of the function.

$$\frac{1 - e^{-(k_{pl} - k_{out}) \cdot t_1}}{k_{pl} - k_{out}}$$

While the procedure followed involves the use of animals different from those in which attempts were made to determine k_{out} values, the factor R occurs only in a correction term, the average effect of which was 10 percent of the finally derived value of k_{out} for para-aminohippuric acid and 7 percent for Rayopake. The error introduced by using a steady-state ratio derived from a supplementary group of animals is therefore negligible so far as the mean values of k_{out} for these substances are concerned. For Diodrast, the correction amounted to an average of 29 percent. Less reliance should be placed, therefore, on the results obtained with this substance.

The experimental determination of the distribution ratio R involves certain mathematical adjustments to take into account the fluctuations in plasma concentration and to make possible the estimation of the steady-state concentration ratio from experiments in which the time was too short for steady state actually to be reached. Repeated plasma samples were taken and the plasma concentration curve was divided into intervals, within which it was assumed that the plasma concen-

tration changed linearly with time. Under this assumption the following formula can be derived:

$$
\begin{aligned}
C_{Aq_n} = &\, C_{Aq_{n-1}} \cdot e^{-k_{out} t_n} \\
&+ R \left(C_{pl_{n-1}} - \frac{S_{pl_n}}{k_{out}} \right) (1 - e^{-k_{out} t_n}) + R S_{pl_n} \cdot t_n
\end{aligned}
\tag{5}
$$

where C_{Aq_n} is the calculated aqueous concentration at the end of the nth interval

$C_{Aq_{n-1}}$ is the calculated aqueous concentration at the beginning of the nth interval

$C_{pl_{n-1}}$ is the calculated plasma concentration at the beginning of the nth interval

t_n is the length of the nth interval

S_{pl_n} is the slope of the plasma curve during the nth interval

k_{out} is the rate of disappearance of the substance from the aqueous

and R is the distribution ratio to be determined.

In applying Equation (5), a start is made with the first interval, where of course the assumption of linear change in plasma concentration is unrealistic. Because of the first exponential term, however, the influence of a distant enough interval on the end result is small. The expected aqueous concentrations are then calculated at the end of each interval, step by step, until the point in time is reached where the actual aqueous samples were taken. The calculated values, which will be expressed as multiples of R are then compared with the observed values for aqueous concentration and R is obtained.

For the computation of R a value of k_{out} has to be known. On the other hand, knowledge of R is necessary for computation of the exact value of k_{out}. The influence of R on k_{out}, and vice versa, is small, however, if the experiment is conducted properly so that the necessary corrections are not large. Then the rough value of k_{out} from Equation (1) can be used in the computation of R with only a small error. This almost correct value of R can then be used to give a nearly correct value of k_{out} which in its turn can be used for an even better value of R, and so forth. In our experiments successive approxima-

tions of this type were not necessary because of the smallness of the corrections. Even in the case of Diodrast a change from the rough k_{out} obtained from Equation (1) to the corrected k_{out} changed the value of R by less than 2 percent of its total.

RESULTS

Figure 1 is a composite from several experiments with para-aminohippuric acid. It shows the concentration of this substance in
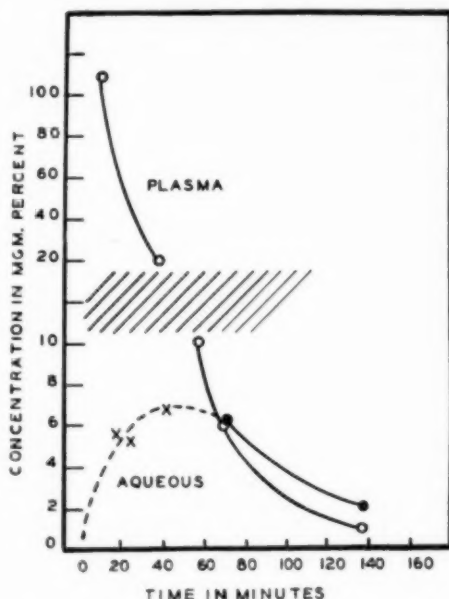

Fig. 1 (Bárány and Kinsey). Concentration of para-aminohippuric acid in the aqueous humor and plasma at various times following intravenous injection.

plasma and aqueous at various periods following intravenous injection. The break in the scale was necessary because of the extremely high concentration of the para-aminohippuric acid in the plasma compared with that in the aqueous during the initial part of the experiment. After sufficient time the concentration in the plasma is so reduced by renal excretion that the aqueous concentration is higher. It is noteworthy, although

not visible in this curve, that after a certain interval the aqueous concentration starts to decrease while the plasma concentration still is above it.

Figure 2 shows the results of five typical experiments plotted on a logarithmic concentration scale. The short lines to the right connect the aqueous concentrations of the right and left eye which were sampled about 60 minutes apart. It is seen that the slopes of the aqueous curves are very similar, indicating similar rates of disappearance.

Table 1 shows relevant data pertaining to 23 experiments in which the rate of disappearance of para-aminohippuric acid was determined. From column 8 it may be seen that
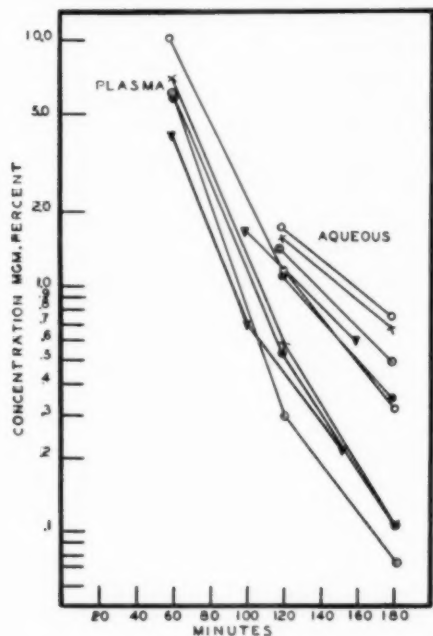

Fig. 2 (Bárány and Kinsey). Logarithm of the concentration of para-aminohippuric acid in the plasma and aqueous of six rabbits at various times after injection.

the mean rate of disappearance is 0.0148. The median rate is 0.0143. These values correspond to a half-life of 47 and 48.5 minutes, respectively. The close correspond-

ence shows that the distribution is fairly symmetrical.

It may be seen from the case numbers that in the few experiments in which the same
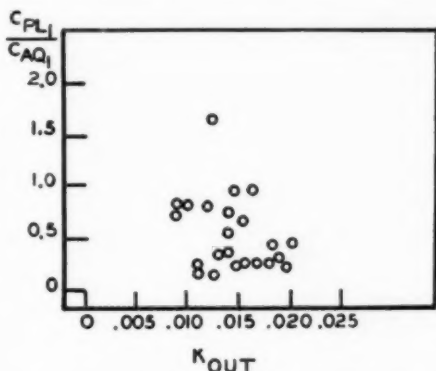

Fig. 3 (Bárány and Kinsey). The ratio of the concentration of para-aminohippuric acid in the first plasma to that in the first aqueous samples as a function of the rate of disappearance (k_{out}) in 23 rabbits.

animal was used twice, the values obtained differ considerably. Each experiment has consequently been used as a statistical unit.

The table also illustrates (compare columns 7 and 8) the magnitude of the correction necessary to take account of the presence of test substance in the plasma. To show that the correction is adequate, a scattergram was prepared (figure 3) by plotting the ratio of the concentration in the first plasma to that in the first aqueous as ordinate against the corrected value for k_{out} as abscissa.

Figure 3 shows that the majority of points form a symmetrical cluster, the corrected rate of disappearance being independent of the plasma concentration at the beginning of the test run. If the uncorrected rates were plotted instead, the cluster would be skewed with its top displaced to the left.

There was no noticeable difference in the half-life of para-aminohippuric acid between light and heavy rabbits and between rabbits used for the first time and those which had been subjected to paracentesis some time

TABLE 1

THE RATE OF DISAPPEARANCE OF PARA-AMINOHIPPURIC ACID FROM THE AQUEOUS HUMOR OF RABBITS

1	2	3	4	5	6	7	8	9
Case	C_{pl_1} (mg. %)	C_{Aq_1} (mg. %)	C_{Aq_2}	Time (Min.)	k_{PL}	k_{out} (uncorrected)	k_{out} (corrected)	$t_{\frac{1}{2}}$ (min.) (corrected)
1	1.70	1.77	0.82	59	0.0267	0.0131	0.0151	46.0
1	1.07	1.92	0.893	62	0.0094	0.0123	0.0140	49.3
2	1.9	2.32	1.20	60	0.0198	0.0110	0.0125	55.4
17	0.92	1.28	0.565	63	0.0289	0.0130	0.0143	48.5
23	1.80	2.42	1.47	60	0.0231	0.0083	0.0092	75.5
25	0.80	1.83	0.64	60	0.0231	0.0175	0.0188	36.9
25	0.31	1.27	0.522	63	0.0064	0.0141	0.0151	45.9
19	0.562	1.24	0.40	60	0.0198	0.0189	0.0205	33.8
19	0.26	1.48	0.77	60	0.0071	0.0109	0.0114	60.8
24	0.64	1.66	0.735	60	0.0231	0.0136	0.0143	48.6
11	0.35	1.53	0.534	60	0.0239	0.0176	0.0183	37.9
4	1.28	1.89	0.81	60	0.0210	0.0141	0.0158	43.0
22	5.8	3.55	1.92	60	0.0239	0.0103	0.0130	53.2
41	5.4	5.60	2.24	63	0.0247	0.0145	0.0168	41.0
49	2.6	2.98	1.77	61	0.0224	0.0086	0.0098	70.6
49	0.71	2.78	1.14	60.5	0.0071	0.0147	0.0157	44.2
30	0.22	0.602	0.28	63	0.0085	0.0122	0.0133	52.1
43	0.87	1.051	0.64	55	0.0173	0.0090	0.0104	66.9
46	0.35	1.17	0.468	58.5	0.0110	0.0157	0.0168	41.3
48	0.18	1.33	0.615	61	0.0094	0.0126	0.0129	53.9
36	0.20	0.662	0.228	60.5	0.0084	0.0176	0.0192	36.1
34	0.20	0.872	0.279	60.5	0.0084	0.0188	0.0200	34.7
40	0.15	0.675	0.348	59.5	0.0069	0.0111	0.0116	59.7
					Average	0.0135	0.0148	47.0
					Median	0.0135	0.0143	48.5

C_{pl_1} is the plasma concentration at the time the aqueous, with concentration C_{Aq_1}, was removed from the first eye. C_{Aq_2} is the concentration in the aqueous of the second eye t_1 minutes later. K_{pl} is the rate constant for disappearance from the blood stream and k_{out} the rough rate constant for disappearance from the aqueous, assuming the blood free from test substance. K_{out}, corrected, is mathematically corrected for presence of test substance in the plasma and $t_{1/2}$ is the half-life corresponding to the corrected rate of disappearance.

earlier. This does not prove that the half-life is independent of, for example, size of eye; it only shows that the unavoidable variability associated with the experiments overshadows minor differences.

In one group of experiments the first aqueous was removed as early as 70 minutes after the intravenous injection and in another as late as 210 minutes. The object of this variation of the standard experiment was to determine whether the half-life might be significantly affected by para-aminohippuric acid coming from or going to the lens and vitreous humor. Thus, it would be expected that since the concentration in the aqueous would build up faster than in the vitreous and lens, the substance would leave the aqueous for these structures during the

earlier intervals following injection; whereas, it would move from them to the aqueous at later times when the concentration of para-aminohippuric acid in the aqueous is falling. No shift in disappearance rate which could be attributed to effects of this kind was discernible, however.

The results of the same type of experiments with the two iodine compounds, Rayopake and Diodrast, are shown in Table 2. Their median rates of disappearance are 0.0125 and 0.0122, respectively. In these experiments every rabbit appears only once in connection with each substance. Approximately half of the animals used with each substance were used for the first time. Figure 4-A and B shows scattergrams of the rate of disappearance as a function of the

plasma/aqueous concentration ratio at the beginning of the experiment, illustrating in the same way as Figure 3 the adequacy of the correction applied for presence of the test substance in the blood.

The scatter of the values obtained with all three test substances may appear high. It must be borne in mind, however, that in addition to the unavoidable errors of volumetry and analysis and the variability between animals, there is a specific source of variability in every experiment where a rate curve is determined by sampling of the two eyes.

It is assumed that the two eyes are identical, but this is not necessarily so. When one eye differs from the other in almost any respect, the result on the rate of disappearance as obtained in experiment can be either an increase or a decrease, even if the respect in which the eyes differ has nothing to do with the parameter studied. Because of this possibility of erratic values, the medians probably more accurately represent the rates of disappearance than do the arithmetic means. As it happens, they differ very little in the present experiments.

The corrections for presence of test sub-

TABLE 2

The rate of disappearance of Rayopake and Diodrast from the aqueous humor of rabbits

| Rayopake k_{out} (corrected)		Diodrast k_{out} (corrected)
0.0125		0.0147
0.0123		0.0160
0.0156		0.0112
0.0073		0.0110
0.0114		0.0127
0.0125		0.0147
0.0129		0.0108
0.0066		0.0089
0.0100		0.0155
0.0086		0.0070
0.0088		0.0029
0.0174		0.0120
0.0133		0.0177
0.0130		0.0083
0.0183		0.0148
0.0128		0.0194
0.0106		0.0122
0.0168		0.0089
0.0052		
0.0149	Mean	0.0122 ± 0.0010
0.0168	Median	0.0122
0.0146		
0.0180		
0.0108		
0.0182		
0.0106		
0.0104		
Average 0.0126 ± 0.0007		
Median 0.0125		
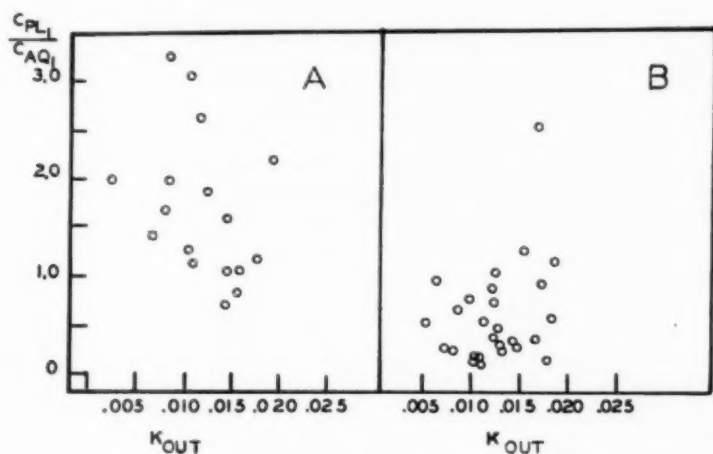
Fig. 4 (Bárány and Kinsey). The ratio of the concentration of Diodrast (A) and Rayopake (B) in the first plasma to that in the first aqueous samples as a function of the rate of disappearance (k_{out}) in 18 and 27 rabbits, respectively.

stance in the blood were made by means of the values for the ratio between the concentration of a substance in the aqueous and that in the plasma when steady state has been reached. These values will also be used in the following paper for calculation of the rate of flow of aqueous.
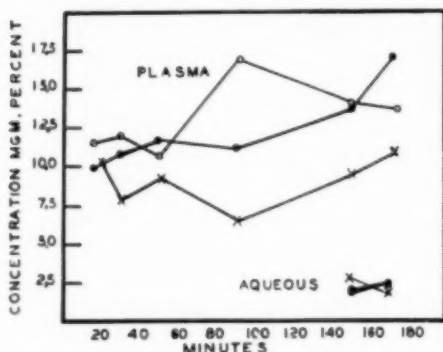
Figure 5 shows three experiments in in-

Fig. 5 (Bárány and Kinsey). The concentration of para-aminohippuric acid in the aqueous humor and plasma of rabbits at various periods following multiple injections.

tact rabbits where the plasma concentration of para-aminohippuric acid was upheld by an initial intravenous injection of 75 mg. immediately followed by an intraperitoneal in-

jection of 300 mg., and then by intraperitoneal injection of 125 mg. every 20 minutes. The difficulties in obtaining a constant plasma level by a schedule of this kind are great, it being considerably easier when the kidneys are tied. This is especially true for Rayopake and Diodrast.

In animals with tied kidneys the Rayopake concentration drops only slowly after the first few hours. In one typical experiment in which 6 animals with tied kidneys had been injected with Rayopake 15 hours earlier, the plasma concentration dropped only 8 percent of its value over a period of 200 minutes. In a corresponding experiment with Diodrast, a fall of about 13 percent was observed.

TABLE 4

STEADY-STATE DISTRIBUTION RATIO OF RAYOPAKE

Dose			
5.6 mg.		50 mg.	
O.S.	O.D.	O.S.	O.D.
0.095	0.089	0.078	0.104
0.100	0.098	0.127	0.120
0.108	0.102	0.127	0.119
0.130	0.132	—	0.123
		0.131	0.145
		0.186	0.167

Mean	0.107		0.130
Median	0.101		0.127
	Grand mean	0.120	
	Grand median	0.120	

TABLE 3

STEADY-STATE DISTRIBUTION RATIO OF
PARA-AMINOHIPPURIC ACID

Normal Rabbits		Rabbits with Tied Kidneys	
O.S.	O.D.	O.S.	O.D.
0.17	0.13	eye tonometrized	0.18
0.14	0.15		0.14
0.23	0.17		0.13
0.18	0.19		—
0.39	0.21		—
0.16	0.19		—

Mean	0.19	Grand mean	0.18
Median	0.17	Grand median	0.17

TABLE 5

STEADY-STATE DISTRIBUTION RATIO OF DIODRAST

O.S.	O.D.
0.078	0.070
0.104	0.095
0.105	0.101
0.142	0.142
0.146	0.151
0.152	0.159
0.179	0.196
0.209	(0.252)*

Mean	0.143
Median	0.144

* The value in parentheses was from an unusually small aqueous sample with large measuring and counting error.

Tables 3, 4, and 5 show the results of the steady-state experiments with the three test substances. The correction formula given in the mathematical section was employed in all instances.

Table 3, giving the para-aminohippuric acid values, shows that kidney ligation experiments lead to distribution ratios within the normal range. This was to be expected. The left eyes of the nephrectomized animals were tonometrized and the tonometer readings were normal.

Table 4 gives the Rayopake values, all obtained with ligated kidneys. The table shows that the amount of actual test substance in the aqueous can be varied as $1:9$ without significantly changing the distribution ratio. This observation is of importance because it justifies the use of linear expressions for the rates of entrance and exit of the substance from the aqueous. If nonlinear relations prevailed here, the distribution ratio would not be constant over a wide range of plasma concentrations.

Diffusion and flow both can be expected to give rise to linear expressions, but for secretion this is not necessarily true. Kinsey[5] has demonstrated the large variation of the distribution ratio for ascorbic acid with varying plasma levels. The proof of linearity for Rayopake is considered to be extendable to the two other substances, too; although, strictly speaking, special experiments would have been required to prove this. Since the method of analysis did not permit the determination of the other two substances at low enough concentrations, the experiments were not carried out.

Surveying the steady-state values in Tables 3, 4, and 5 the relatively good check between the two eyes, as compared with the significant variation between animals, is noticeable. The large variability between different animals makes comparisons between the values obtained for the three substances difficult. One would have expected Diodrast, which has the highest molecular weight, to

have the lowest distribution ratio. That this was not found may be due to random variation. On the other hand, it is possible that the Diodrast molecule is so large that it is held back to some extent at the filtering angle. This would increase the steady-state concentration.

The method used here to determine rate of disappearance of a substance from the aqueous is very similar to that used by Abe and Komura. These authors, too, watched the disappearance of their test substance from aqueous some time after an intravenous injection. They made no correction for the presence of test substance in the blood, however, but assumed that as soon as the fluorescein concentration in the aqueous had dropped to lower than one fortieth of that in the plasma, there was no passage of fluorescein into the aqueous any longer. Their figure, one fortieth, was supposed to be the fraction of fluorescein freely diffusible. The rates of disappearance observed by these authors thus are systematically too low. Moreover, since they worked with atropinized eyes a comparison with our values has no point.

SUMMARY

In order to obtain a value for the rate of flow of aqueous, the rates of disappearance from the aqueous of three test substances which could be expected to leave the aqueous mainly by flow were measured. The test substances were para-aminohippuric acid, Rayopake, and Diodrast. They are able to enter the aqueous from the blood stream. They are excreted by the kidneys at maximal rate, so that the plasma concentration after an intravenous injection shows a very sharp drop. Some time after the injection, therefore, the substances disappear from the aqueous at a rate which is only to a small extent influenced by simultaneous replacement from the blood. A mathematical treatment taking this replacement into account was worked out. The rates of disappearance

(k_{out}), as they would have been found if the blood stream were free of test substance, were para-aminohippuric acid, 0.0143; Rayopake, 0.0125; and Diodrast, 0.0122.

The steady-state distribution ratio aqueous/plasma was measured, using a mathematical correction taking fluctuations of plasma level of the test substance into account. The median distribution ratios were para-aminohippuric acid, 0.17; Rayopake, 0.12; and Diodrast 0.14.

The distribution ratio for Rayopake was independent of large variations in the concentration of the substance, showing that essentially linear conditions prevail with respect to exit and entrance of this substance.

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THE RATE OF FLOW OF AQUEOUS HUMOR*

II. DERIVATION OF RATE OF FLOW AND ITS PHYSIOLOGIC SIGNIFICANCE

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In the preceding paper,[1] the authors reported values, in rabbits, for the rate of disappearance of three test substances from the anterior chamber and the ratio of their concentrations in the aqueous humor[§] to those in the plasma under steady-state conditions. The object of the present paper is to utilize these data to derive the rate of flow of aqueous humor and in turn to use the derived value for determining how various substances, including sodium and chloride, enter the anterior chamber.

One of the postulates of the theory of intraocular fluid dynamics advanced by Kinsey and Grant[2] is that all nonmetabolized substances in the aqueous humor leave by flow, and may, in addition, leave by diffusion. Thus, the rates of disappearance are thought to consist of a rate of flow, and also, in the case of some substances, a rate of diffusion. An exact value for the rate of flow of aqueous humor cannot be derived, therefore, from the rate of disappearance of a single test substance without knowing whether the substance can diffuse out of the anterior chamber.

Information of this kind, however, is equivalent to knowing how the substance enters the anterior chamber. There are two main possibilities. If the substance is capable of entering the anterior chamber only as a result of a secretory process, and not

by diffusion, it can leave only by flow. The rate of disappearance and rate of flow will then be the same, assuming, as the authors do, that no secretion out of the eye occurs, and that the substance is not metabolized.

The other possibility is that the substance is capable of entering the anterior chamber entirely, or in part, by diffusion. Then it is also capable of leaving it by diffusion. In this instance some of the loss out of the anterior chamber will occur as a result of diffusion, and the rate of disappearance will be made up of a rate of diffusion, as well as a rate of flow, as stated above.

The rate of flow in this instance is less than the rate of disappearance. Thus, knowledge of the rate of disappearance of the test substance permits calculation of a maximum and minimum value for rate of flow corresponding to entrance by secretion[∥] only, or by diffusion only, respectively. When both secretion and diffusion occur, intermediate values for rate of flow are obtained.

In order to obtain the rate of flow, we attempted to circumvent the lack of knowledge of how most compounds enter the anterior chamber by determining the rate of disappearance of substances of relatively high molecular weights. Through the use of such substances, the contribution of diffusion, if any, to the loss from the aqueous humor can be expected to be small, and consequently the limits between which the actual flow rate

∥ Secretion is used in the broad sense of unidirectional transfer of substances into the anterior chamber as a result of an expenditure of energy. The source of the energy and the site of any secretory activity, more than to say that they must lie toward the ciliary body from the anterior chamber, do not enter the argument at this point.

lies would be narrow. In addition to the large size, the substances selected were of graded molecular weights, it being thought that still more exact information concerning the rate of flow might be obtained by extrapolation, in the event that the rate of disappearance was found to decrease progressively with increase in molecular weight. Inherent in the argument, of course, is the assumption that the test substances are not preferentially prevented from leaving the anterior chamber by flow.

The rate of flow of aqueous humor within the limits referred to above can readily be derived from the rate of disappearance of a test substance by use of equations formulated by Kinsey and Grant[2] to describe entrance and exit of constituents from the anterior chamber when these enter either by diffusion or secretion. The relations may be more apparent from the equation representing the rate of disappearance and rate of entrance by any means, as used by Palm[3] and employed by Bárány and Kinsey.[1] The latter is:

$$(1) \qquad \frac{dC_{Aq}}{dt} = k_{in}C_{pl} - k_{out}C_{Aq}$$

where C_{Aq} and C_{Pl} are the concentration in the aqueous humor and plasma, respectively; k_{in} is the rate of entrance and k_{out} the rate of disappearance. At steady state, when the rate of change of C_{Aq} equals zero, this gives

$$(1a) \qquad \frac{k_{in}}{k_{out}} = \left(\frac{C_{Aq}}{C_{pl}}\right)_{Steady\ state} = R$$

whence:

$$(1b) \qquad k_{in} = Rk_{out}$$

where R is the steady-state distribution ratio aqueous/plasma. When entrance occurs by secretion:

$$(2)^* \qquad k_{in} = k_{secr.}$$
and
$$k_{out} = k_{flow}$$

* The subscripts used by Kinsey and Grant[2] have been changed as follows: In (2) k_2 to $k_{secr.}$; in (3) k' to k_{flow} and k_2 to $k_{secr.}$. The subscript abbreviations diff. and secr. refer to diffusion and secretion, respectively.

where $k_{secr.}$ is the rate of entrance by secretion and k_{flow} the rate of loss by flow.

When entrance occurs by diffusion:

$$k_{in} = k_{diff.}$$

but

$$(3) \qquad k_{out} = k_{diff.} + k_{flow}$$

where $k_{diff.}$ is the rate of entrance and exit by diffusion. Steady state then is:

$$(4) \qquad \frac{k_{diff.}}{k_{diff.} + k_{flow}} = \left(\frac{C_{Aq}}{C_{pl}}\right)_{Steady\ State} = R$$

which gives

$$(5) \qquad k_{flow} = k_{out}(1-R).$$

Since it was proposed to calculate the rate of flow of aqueous humor from the rate of disappearance of a test substance on the basis of the concepts already set forth and represented mathematically by the above equations, and since the validity of Equation (4) and the differential equation from which it has been derived have been questioned, some discussion of these concepts seems warranted.

Duke-Elder and Davson[4] disagree with the concept described by Kinsey and Grant's Equation (4) above. The latter represents entrance into the anterior chamber by diffusion and exit by flow. They state that energy would have to be supplied if fluid lost by flow were not replaced by fluid having the same concentration of the substance in question as found in the blood. They argue that, since, under the conditions of dialysis and ultrafiltration, there would be, at best, only small amounts of energy available, the situation must be described by their Equation (5) which, with symbols changed to conform with those used elsewhere in this paper, is reproduced below.

$$\frac{dC_{Aq}}{dt} = k_{diff.}(C_{pl} - C_{Aq}) - k_{flow} \cdot C_{Aq} + k_{flow}C_{pl}$$

from which the following is obtained

$$\frac{k_{diff.} + k_{flow}}{k_{diff.} + k_{flow}} = \left(\frac{C_{Aq}}{C_{pl}}\right)_{Steady\ State} = R = 1.0$$

Under these conditions they point out that the ratio of the concentration in the

aqueous humor to that in the plasma at steady state must always be unity. The objection to their argument is that their equation describes a situation in which there is a unidirectional force moving constituents of aqueous humor through the membrane under steady-state conditions, namely flow of fluid through the membrane. Since this is *not* dialysis, by definition, it represents a situation different from that which Kinsey and Grant were considering, and therefore is not relevant to the argument that flow, in the presence of dialysis, could account for steady-state ratios below 1.0. It is clear that energy would have to be supplied to keep the aqueous humor flowing, but it does not follow that the diffusion equation of Kinsey and Grant is erroneous. The equation given by the latter workers simply describes what would happen to a substance diffusing into the anterior chamber in the presence of flow out of the anterior chamber. The source of energy required to maintain this flow does not enter the problem at this stage.

Since it is apparent that the separation of water from its solutes would require energy (indeed more energy than can be provided by the filtering blood pressure), it follows that if the constituents of aqueous humor entered only by diffusion, that is, when no excess energy is supplied, there could be only an insignificant flow.

Thus, if no energy is supplied one is at a loss to explain the low distribution ratio of such substances as urea and levulose, which was the original objective of testing the consequences of the flow hypothesis, not to speak of the very low ratios observed with the test substances used by the present investigators.

Subsequent criticism of Equation (4) is of a different kind. It is contained in the statement by Davson[5] that "this equation has been shown to involve a simple mathematical error which completely invalidates it. . . ." He cites the above-mentioned paper of Duke-Elder and Davson[4] as a reference. There is, however, no mention in the paper

by Duke-Elder and Davson of a "simple mathematical error."

Furthermore, reference is made in [5] only to the paper of Duke-Elder and Davson and not to a paper of Kinsey and Grant[6] in which rebuttal is made to the former's disagreement with the concepts involved, giving the reader who is unfamiliar with the literature on the subject the erroneous impression that the whole original concept is now an admitted mistake because of an error in mathematics. The paper referred to by Davson contains no reference to the specific rules of mathematics which are violated and we maintain that Equation (4) is mathematically sound.

Without specific assumption of secretion, Palm[3] proposes the following more general expression intended to take into account the possibility that the fluid which replaces that lost by flow contains the substance in a fraction α of the concentration found in the plasma. His equation, with altered subscripts, is:

$$(6) \qquad \frac{dC_{Aq}}{dt} = k_{diff.}(C_{pl} - C_{Aq}) + \alpha k_{flow} C_{pl} - k_{flow} \cdot C_{Aq}$$

where, according to Palm, α denotes the ratio of the rates of passage of the substance and water through the membrane. Under these conditions the distribution ratio becomes

$$(7) \qquad \frac{k_{diff.} + \alpha k_{flow}}{k_{diff.} + k_{flow}} = \left(\frac{C_{Aq}}{C_{pl}}\right)_{Steady\ State} = R$$

whence

$$(8) \qquad k_{flow} = k_{out}\left(\frac{1-R}{1-\alpha}\right).$$

Inspection of Equation (8) shows that when α is >1, R must also be >1, and thus the concentration in the aqueous humor would be greater than in the plasma, which is opposed to the original assumption of entrance by diffusion. When α is <1 it cannot exceed R and it can equal R only when there is no diffusion. Since there is no way of evaluating α the derivation of k_{flow} from k_{out} has been carried out on the assumption that $\alpha = 0$. If α were considered to have

TABLE 1

THE MEDIAN RATES OF DISAPPEARANCE AND RATIOS OF CONCENTRATION IN THE AQUEOUS
HUMOR TO THAT IN THE PLASMA WATER

Test Substance	Mol. Wt.	No. of Expts.	k_{out}	$\left(\dfrac{C_{Aq}}{C_{Pl}}\right) = R^*$ steady state
Para-aminohippuric acid	194	23	$.0143 \pm .0007$†	0.21
Rayopake	308	27	$.0125 \pm .0007$	0.12
Diodrast	405	18	$.0122 \pm .0010$	0.16

* The ratios are calculated on a kg. of water basis assuming the water content of the plasma to be 93 percent, and adjusted to take into account the fraction of the substance bound to plasma protein. The latter correction was based on dialysis experiments. The fraction bound was 23 percent, 4 percent, and 17 percent, respectively, for para-aminohippuric acid, Rayopake, and Diodrast. (Six experiments with each in cellophane bags.)

† The standard errors are those for the means.

some positive value, the lower limit of the rate of flow would become raised, that is, would approach that given on the assumption of entrance by secretion, and the limits between which k_{flow} must lie become narrower. Thus, the limits for flow obtained by the calculations, which follow are too wide, and are therefore conservative.

The median rates of disappearance (k_{out}) and ratios of concentration in the aqueous humor to that in the plasma water at steady state for the three test substances—para-aminohippuric acid, Rayopake, and Diodrast —are given in Table 1.

The rate of flow can be calculated from the k_{out} values assuming entrance into the anterior chamber by either secretion or diffusion. When the substances are assumed to enter by secretion, k_{out} and k_{flow} are the same, so that no calculation is required to obtain the upper limit for the rate of flow. When entrance is assumed to occur by diffusion, the calculation is carried out with

TABLE 2
EXTREME LIMITS FOR k_{flow}

Test Substance	Assumed Entrance By:	
	Secretion	Diffusion
	k_{flow}	k_{flow}
Para-aminohippuric acid	0.0143	0.0113
Rayopake	0.0125	0.0110
Diodrast	0.0122	0.0102

Equation (5). This gives the lower limit for the rate of flow. The results are tabulated in Table 2.

The extreme limits for k_{flow}, as shown in Table 2, are 0.0102 and 0.0143 as derived from the rate of disappearance of Diodrast, assuming entrance by diffusion, and para-aminohippuric acid, assuming entrance by secretion, respectively. The values for k_{flow}, assuming that all of the substances enter by diffusion, vary only between 0.0102 and 0.0113. Consideration of all of the evidence would suggest that k_{flow} in rabbits must be very close to 0.011. This means that 1.1 percent of the total volume of aqueous humor in the anterior chamber leaves by flow every minute. For an average anterior chamber having a volume of 250 cubic mm., this corresponds to 2.75 cu.mm./min.

Because of the through and through circulation in the eye (flow), all constituents of the aqueous humor which are not preferentially held back at the filtering angle must disappear from the anterior chamber with at least this basal rate. If they are able to exchange between blood and aqueous humor in the anterior chamber by other means, their rates of disappearance will be higher than the basal rate, that is, the rate of exchange by diffusion will be added to the flow rate (equation 4) (see also fig. 4). Information concerning the magnitude of the rate of flow in conjunction with a value for the rate of disappearance of a substance can, there-

fore, be used to draw inferences regarding the role of diffusion in the entrance of the substance into the anterior chamber. The following discussion (based on this type of reasoning) will be concerned with conclusions which can be drawn concerning the mode of entrance of the chief electrolytes of the aqueous humor, sodium and chloride, and certain other substances.

In previous studies, Kinsey and Grant[7] found that the half-life of sodium in the anterior chamber of rabbits was approximately 50 minutes, which corresponds to a k_{out} of 0.0140. In making their calculations they assumed a steady-state distribution ratio for sodium of 0.90. We have determined experimentally the steady-state ratio for so-

TABLE 3

THE RATIO OF THE CONCENTRATION OF SODIUM IN THE AQUEOUS HUMOR TO THAT IN THE PLASMA WATER* AT STEADY STATE

	Eye	
	O.S.	O.D.
	0.84	0.89
	0.93	—
	0.99	0.94
	0.88	0.95
	1.14	0.94
	0.93	0.95
	0.96	0.975
	0.87	0.89
	0.925	0.925
Mean	0.94	0.935
Mean O.U.		0.94
Median O.U.		0.93

* The water content of plasma was assumed to be 93 percent by volume.

dium in rabbits by injecting radioactive sodium (Na24) and, 13 hours later, determining the relative concentration in the anterior chamber and plasma. The data for the steady-state values are shown in Table 3.

Table 3 shows that the median value for the steady-state ratio of sodium is 0.93. Using this value and the data reported previously by Kinsey and Grant,[7] the rate of disappearance of sodium in the anterior chamber was determined by plotting the logarithm of the difference between the ob-

served value and that reached at steady state against time, once the sodium level in the blood had become constant (fig. 1). This method of treating the data is based on the fact that, in the case of isotopes, at steady state, the rate of accumulation of one isotope is a measure of the rate of disappearance of
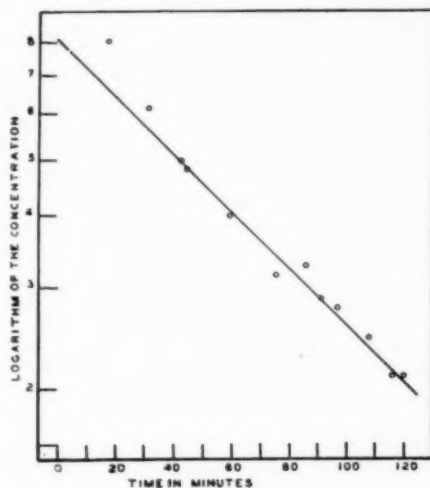

Fig. 1 (Kinsey and Bárány). Disappearance of sodium from the aqueous humor of the rabbit eye.

the other isotope present. In the present instance, the rate of accumulation of trace amounts of Na24 was measured, assuming that the body does not differentiate between Na24 and the normally present isotope Na23; this is equivalent to measuring the rate of disappearance of the latter ion.

Figure 1 shows that the experimental values obtained at times earlier than 40 minutes fall above the line. The initial rapid rise in concentration of radioactive sodium in the anterior chamber may be due to insufficient stirring of the aqueous humor so that loss of the tracer sodium by flow is at first abnormally low with the result that the concentration of radioactive sodium in the aqueous humor increases too rapidly at first, and gives the appearance of a short half-life. Palm[3] was the first to point this out. More-

over, it will be seen from the figure that, although the concentration is rising too rapidly, the actual concentrations are too low. This may be explained simply by the fact that the blood levels have not yet reached their steady state. The half-life of sodium, once constant rate has been reached, is 61 minutes. This corresponds to a k_{out} value for sodium of 0.0113.

The difference between the k_{out} values as given above, namely, 0.0113 and that found previously, namely, 0.0140, is due partly to

TABLE 4
COMPARISON OF RATE OF FLOW AND RATE OF DISAPPEARANCE

Organic Test Substance Assumed to Enter By:	Aver., Weighted for No. of Determinations, Para-aminohippuric Acid, Rayopake, and Diodrast	So-dium
	k_{flow}	k_{out}
Diffusion	0.0109	0.0108
Secretion	0.0130	

the use by Kinsey and Grant[2] of a steady-state distribution ratio of 0.90 instead of 0.93, and partly to utilizing the experimental points obtained at earlier times when the concentration was changing too rapidly.

To obtain further data on the rate of disappearance of sodium from the anterior chamber of rabbits, five additional experiments were carried out. The injections of radioactive sodium were given intraperitoneally, and blood and samples of aqueous humor from one eye, and then the other, were taken at approximately 45 and 100 minutes. The plasma levels used to calculate the half-lives were the mean of the two plasma concentrations at the moment of aqueous-humor withdrawal which was timed to occur after the plasma concentration of radioactive sodium was essentially constant. The rates of disappearance calculated from these experiments are represented by the k_{out} values 0.0119, 0.0115, 0.0099, 0.0099, and 0.0087. This represents an average k_{out}

value of 0.0104 with an average for all the sodium results of 0.0108.

The value for the rate of disappearance of sodium can now be compared with the rate of disappearance which must be imposed by flow on all constituents of aqueous humor, excepting, of course, any held back at the filtering angle, for example, protein. As previously indicated, because of the lack of knowledge of the exact mode of entrance of the three organic test substances, there is some uncertainty as to the exact value of the rate of flow. Accordingly, the average values for k_{flow}, assuming entrance either by diffusion or secretion, will be used in making the comparison. The data are presented in Table 4.

The close correspondence between the rate of disappearance of sodium and rate of flow, as obtained by the three test substances on the basis of assumed entrance by either diffusion or secretion, is evident from the data given in Table 4. A quantitative estimate for the rate of loss by diffusion (k_{diff}) for sodium can be calculated by insertion of the experimental values into Equation (4). K_{diff} for sodium is found to equal -0.0001 or -0.0022 for assumed entrance of the organic ions by diffusion or secretion, respectively. The almost precise agreement between the rate of disappearance of sodium (k_{out}) and the rate of flow (on the assumption that the organic test substances entered by diffusion), is fortuitous, considering the magnitude of the individual variations in rate constants.

For the same reason the definitely negative value for loss by diffusion of sodium, assuming entrance of the test substances by secretion, does not necessarily preclude the possibility that the test substances enter by this means, even if it favors the idea that the test substances enter by diffusion. The experiments show unequivocally, however, that *any loss of sodium from the aqueous humor by diffusion must be so small as to be within the experimental errors involved, and very much smaller than the loss by flow.*

Thus for sodium:

$$k_{diff.} \lll k_{flow.}$$

The question now arises as to what inferences can be drawn from these results with regard to the rate and mode of *entrance* of sodium. It might be thought that if but a small proportion of the total amount of a substance leaves the aqueous humor by diffusion, as is the case for sodium, the substance could not enter solely by diffusion and the conclusion could be drawn immediately that the substance must enter by an active process. That this is not the case, however, can be seen from the following consideration.

If there were only a small concentration of the substance in the aqueous humor so that the total *quantity* of substance lost by flow each minute would be small, the substance might well be replaced from the blood by diffusion, provided the plasma concentration, and thus the driving concentration difference, were sufficiently large, even if the diffusibility were low. Thus, entrance by only diffusion is compatible with exit predominantly by flow, but then the steady-state distribution ratio aqueous/plasma will be low. The organic test substances used in the present experiments are probable examples.

In the case of sodium, however, the concentration in the aqueous humor is nearly the same as in the plasma, and the driving concentration difference is consequently small, too small in fact, to account for the loss by flow. Moreover, since the diffusibility through the membrane is low, as shown above, complete replacement of the lost sodium by diffusion is not possible; sodium must, therefore, enter the aqueous humor predominantly by some other process. The same reasoning expressed in symbols:

According to Equation (1b)

$$k_{in} = R k_{out.}$$

for sodium R is 0.93, thus

$$k_{in} = 0.93 \cdot k_{out.}$$

Since 0.93 is near unity and we have

shown above that $k_{diff.} \ll k_{out}$ for sodium, it follows that $k_{diff.} \ll k_{in}$ too. Thus, diffusion can at most play a minor part in the entrance of sodium into the aqueous humor.

The discussion of flow up to now has been based on comparison between values obtained in different groups of animals. To eliminate this difference, the authors carried out a smaller number of experiments in which the rate of disappearance of Rayopake or Diodrast from the anterior chamber and the rate of accumulation of radioactive sodium in this chamber were determined simultaneously in the same animal.

For this purpose rabbits were selected which were as dissimilar as possible. Some animals had never been used before, several had been injected with radioactive compounds previously, several were large (3 to 3½ kg.), and several were small (1.2 to 1.4 kg.).

Separate assay of the sodium and iodine compounds in the aqueous humor and plasma samples was accomplished by measuring the radioactivity through sufficient absorbing material to eliminate all but an insignificant part of the radiations arising from the iodine, and then remeasuring the activity, without filters, a week later when the radiations from the sodium had decayed to an insignificant portion. After correction for radioactive decay, the first measurement indicates the amount of sodium, and the second measurement the amount of the iodine compound, which is present. The sodium was injected 60 minutes after the iodine compound, the first sample was withdrawn 40 minutes later, and the second sample one hour after the first sample.

The resulting values of k_{flow}, calculated on the basis of assumed entrance by diffusion or secretion of the organic ion, and the k_{out} values for sodium are shown plotted as scattergrams in Figures 2 and 3, respectively. The lines illustrate what would be theoretically perfect correlation. With one notable exception the data show a reasonable correlation between the k_{flow} values calcu-

lated from the Rayopake (open circles), and Diodrast (filled circles), and the k_{out} values for sodium.

Presumably because the animals in this group were so variable, there was a considerable spread between the results obtained with individual animals, particularly in the
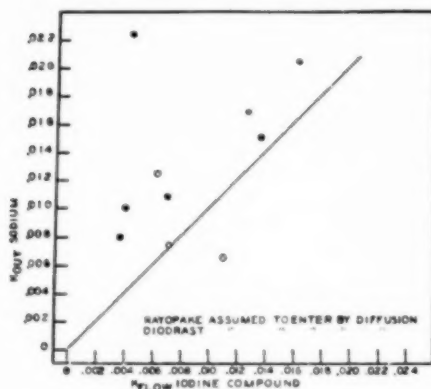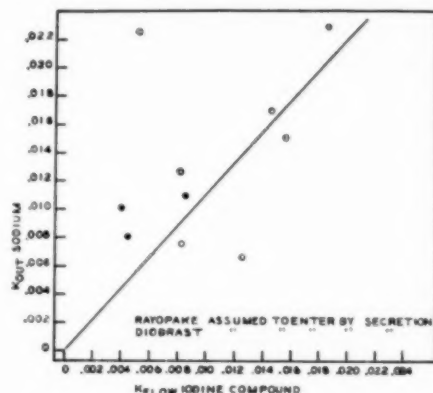

Fig. 2 (Kinsey and Bárány). Rate of disappearance of sodium and rate of flow as determined simultaneously with Rayopake or Diodrast assuming entrance of the organic compounds by diffusion.

case of k_{out} values for sodium. There is a tendency for the k_{out} values for the sodium to be slightly higher than the k_{flow} values for the organic ions. This difference is of questionable significance, but could be explained on the assumption that a small proportion of the sodium diffuses out of the anterior chamber.

On principle, the same method of reasoning which has been applied for sodium holds for any substance, once the rate of flow is known. The reasoning can be simplified by plotting the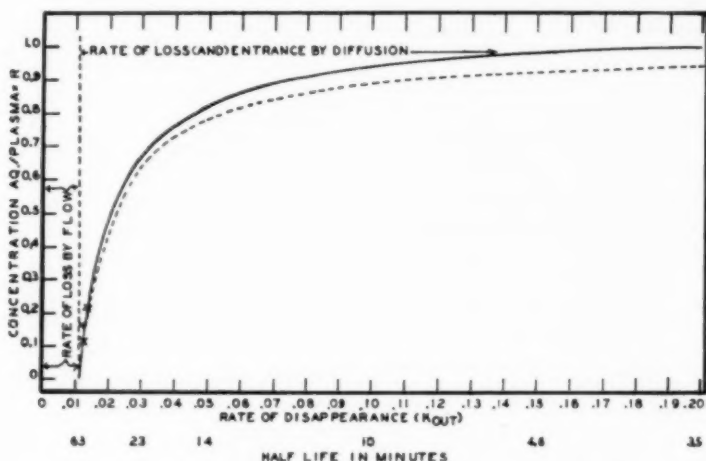 general relation between the steady-state distribution ratio R and the rate of disappearance k_{out} for any substance assumed to enter the anterior chamber only by diffusion.

This relation can be shown graphically by substituting the value 0.011 for k_{flow} in Equation (4) and plotting the steady-state ratio R against k_{out}. Equation (4) contains the inherent assumption that the re-

placement fluid is free from the particular solute in question.

Although, as stated earlier in this paper, it is not possible to evaluate exactly the fractional term z introduced by Palm to take account of solute entering along with water, one can make the assumption that z is equal

Fig. 3 (Kinsey and Bárány). Rate of disappearance of sodium and rate of flow as determined simultaneously with Rayopake or Diodrast assuming entrance of the organic compounds by secretion.

to the ratio of the rates of passage by diffusion of the substance and water through that part of the blood-aqueous barrier concerned with diffusion into the anterior chamber. This might well be a reasonable approximation to the true value of z.

Accordingly, this value, that is, $k_{diff.\ solute}/k_{diff.\ H_2O}$, where $k_{diff.\ H_2O}$ is approximately 0.20 (see Kinsey and co-workers[*]). was set equal to z and k_{flow} equal to 0.011 in Equations (7) and (8) with the following result:

(9) $$R = \frac{1.055 \cdot k_{out} - 0.0116}{k_{out}}.$$

The broken and solid curved lines of Figure 4 represent a plot of Equations (4) and (9), respectively. The perpendicular broken line graphically represents the circumstance in which the substance enters by secretion and leaves only by flow, Equation

(2). In this instance, it is clear that the rate of disappearance will not exceed that given by the rate of flow, irrespective of the steady-state ratio. For convenience the units of the abscissa are expressed as both k_{out} values and as half-lives.

The distance to the left of the perpendicular line of Figure 4 shows graphically the rate of disappearance imposed by flow on all substances not held back preferentially

crosses shown on Figure 4 represent the experimental values found by the authors for the rate of disappearance of the three organic substances tested.

The lines of Figure 4 represent the general situation describing both entrance and exit from the anterior chamber irrespective of whether a substance enters by secretion or any other active process alone and leaves only by flow, or enters by diffusion alone

Fig. 4 (Kinsey and Bárány). The relation between steady-state distribution ratio R and the rate of disappearance k_{out} for any substance assumed to enter the anterior chamber either by diffusion (curved lines) or secretion (broken perpendicular line). (For difference between solid and broken curved lines see text.)

at the angle, and the distance to the right of the line shows the contribution of diffusion to the rate of disappearance. Obviously, a comparison of the magnitude of the distances to the left and right of the line shows the comparative contribution of flow and diffusion to the rate of disappearance. Since diffusion is a two-way process, the distance to the right of the line also represents the rate constant for entrance by diffusion for any particular substance. The distance between the solid curved line and the broken curved line represents the magnitude of the entrance due to bulk filtration as indicated by the alpha term previously referred to. The three

and leaves by diffusion and flow.

Reference to the graph, therefore, permits deductions to be drawn conveniently concerning the mode of entrance of any non-metabolized substance whose rate of disappearance and steady-state distribution ratio are known. If it enters exclusively by secretion or diffusion, its point will fall near to or upon one or the other line. If it enters by both mechanisms, its point will fall somewhere in the field between the two lines. Figure 5 is a graphic construction showing how in this general case the various rate constants can be found once R and k_{out} for a substance are known. The construction is

valid only if the active transport mechanism is linear, so that one can write:

$$k_{in} = k_{diff} + k_{secr} \; ;$$

The situation with respect to sodium has been discussed above. Now it can be considered again as an illustration of the use of Figure 4. Sodium has a steady-state value of 0.93 and a rate of disappearance of 0.0108. The only point on the graphs corresponding to these values appears along the secretion line indicating that sodium must enter the anterior chamber solely by secretion and
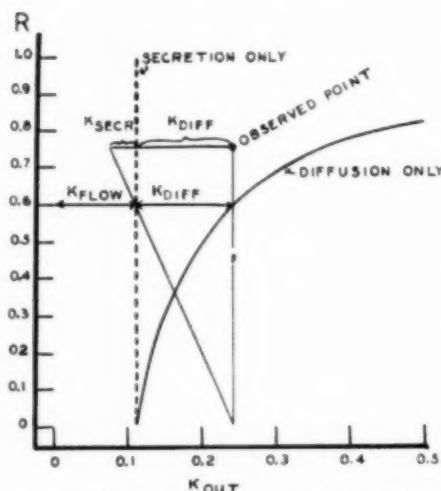
Fig. 5 (Kinsey and Bárány). Graphic method of determining mode of entrance and exit from the anterior chamber given the steady-state distribution ratio and the rate of accumulation in the anterior chamber.

therefore leave solely by flow. In order for it to enter by diffusion and have a steady-state ratio of 0.93, it would have to disappear with a rate of approximately 0.10, or half of that of water, instead of the observed rate of one tenth of this amount.

Kinsey and Grant[7] have shown that the half-life of chloride cannot be very different from that of sodium, and Kinsey[9] has found that in rabbits it has a steady-state distribution ratio of 1.0. Therefore, it follows that

chloride too cannot enter to any significant extent by diffusion, but enters primarily, if not exclusively, by a secretory process at about the same rate as sodium. Similar results are obtained for thiocyanate, the half-life of which was determined by Kinsey and Grant. The values for phosphate (Palm[10]), together with our present values for the rate of flow, show that phosphate too must enter mainly by secretion. Palm states, in effect, that if phosphate is secreted into the aqueous humor and removed by flow, k_{flow} has to be 0.01 to fit his data. On the other hand, if phosphate entered by diffusion, k_{flow} would have to be 0.005. Since our value of k_{flow} is 0.011 it is obvious that his values show that phosphate enters the anterior chamber by secretion.

From the conclusions drawn thus far it may seem that the mode of reasoning adopted leads to the conclusion that all substances, except water, enter the anterior chamber by secretion. That this is not the case may be seen from consideration of ethyl alcohol. Palm[3] has investigated the rate of accumulation of ethyl alcohol in the aqueous humor and found it to be approximately one half of that of water, that is, k_{in} equals 0.10. Since the steady-state value for alcohol was found to be about 1.0, k_{out} must be of the order of 0.10. Figure 4 shows that ethyl alcohol must enter mainly by diffusion. From the figure, the predicted steady-state distribution ratio would be approximately 0.95, a value compatible with Palm's results. Because of lack of mixing in the aqueous humor, and for other reasons throughly discussed in Palm's paper, assignment of precise values for the rate constants of substances entering the anterior chamber as rapidly as ethyl alcohol is not possible. It is sufficient to point out here that ethyl alcohol enters the anterior chamber primarily by diffusion, the mode of entrance which is assumed by Palm.

In rabbits, ascorbic acid has a steady-state distribution ratio of approximately 15, at

physiologic plasma concentrations.[11] We have found (in unpublished work,) that the rate of disappearance from the anterior chamber of rabbits is approximately 0.01.

In this instance the enormously large concentration in the aqueous humor compared with that in the plasma is presumptive evidence of secretion, although Mueller and Buschke[12] have postulated that the ascorbic acid in the aqueous humor comes from the reduction of dehydroascorbic acid by the lens. If ascorbic acid enters the aqueous humor as such from the blood, and is freely diffusible in the aqueous humor, reference to the figure indicates that it must do so mainly by secretion. If it is formed from a precursor, as Mueller and Buschke suggest, its rate of disappearance shows that it leaves entirely by flow—a secondary assumption of the theory of Mueller and Buschke. It is not possible from the present data to choose between the alternatives that ascorbic acid is secreted as such or that it is formed from dehydroascorbic acid.

As stated earlier in this paper, it was in part to explain the steady-state values of urea and levulose that Kinsey and Grant formulated the postulates embodied in Figure 4. Many observers have investigated the steady-state ratio of concentrations for urea; the most recent value, based on 13 rabbits, given by Kinsey and Robison[13] is 0.88. Bárány and Ross[14] have found a ratio of 0.75 in a series of 10 rabbits. Using the average of these values the steady-state distribution ratio is 0.82. Accordingly, if urea were to enter by diffusion, as originally assumed by Kinsey and Grant, it would have to disappear from the anterior chamber with a k_{out} equal to approximately 0.050, or have a half-life of approximately 14 minutes. Recent experiments by Kinsey in a small number of rabbits (4) have given a half-life of approximately 17 minutes, $k_{out} = 0.04$. In view of the small number of available rate experiments the observed half-life is compatible with that derived under diffusion assump-

tions, and it may be concluded that a large proportion of urea must enter by diffusion.

In summary, within the limits of accuracy imposed by experimental variables and variations between animals, the inorganic ions sodium, chloride, thiocyanate, and phosphate enter the anterior chamber predominantly by secretion; whereas, the nonelectrolytes, ethyl alcohol and urea, both enter the anterior chamber primarily, if not exclusively, by diffusion. For the large organic ions used as test substances this question must be left open. The same is true for ascorbic acid because of its special properties. All these substances leave by flow, and those entering by diffusion must in addition leave by diffusion. These conclusions in regard to nonelectrolytes and inorganic ions are the same as those reached previously by Kinsey and Grant, but, because of the relatively precise knowledge of the rate of flow, they can now be considered as established quantitatively within the limits given above.

It is to be noted, however, that the two nonelectrolytes shown to enter mainly by diffusion are known to penetrate cell walls with special ease. It may be that the high rate of entrance by diffusion masks any simultaneous but slower entrance by the same mechanism that transports the various ions. If the mechanism is highly unspecific, it might transport certain nonelectrolytes too.

This leads to the question as to the nature of the mechanism for transporting solutes into the aqueous humor. A detailed discussion of this subject is beyond the scope of this paper; however, several limitations to the application of the findings presented here to the mechanism problem should be stressed. Analyses made on samples of aqueous humor provide information primarily, if not exclusively, on aqueous humor as it exists in the anterior chamber, since the contribution of aqueous humor from the posterior chamber to samples withdrawn for analysis must be small indeed. In so far as the substance analyzed, for instance water or

urea, diffuses into the anterior chamber across the iris-blood barrier, such analytical information immediately enables one to draw inferences with regard to the mechanism by which the substance is transferred from blood to aqueous humor.

For substances like sodium and chloride, on the other hand, which we have shown do not diffuse appreciably into or out of the anterior chamber from the iris (so must pass from the posterior to anterior chamber through the narrow space between iris and lens), it is only possible to state that they enter the anterior chamber by an active process.

Since there is a continuous flow of fluid from the posterior to the anterior chamber, this flow of fluid is probably the active and unidirectional mechanism by means of which the substances are transported into the anterior chamber, and which, in the sense of the term as used here, has been called secretion. If this be true, the limiting factor for the rate of entrance of many solutes into the anterior chamber may not be the transport from plasma to aqueous humor in the posterior chamber through the ciliary epithelium, but the rate at which they are carried into the anterior chamber by a flow of water.

Since the flow of water requires energy for its maintenance, clearly it is essential that some substance or substances, but not necessarily either sodium and/or chloride (which might diffuse back and forth between the plasma and aqueous humor in the posterior chamber), be actively transferred into the posterior chamber from the plasma. Perhaps the simplest means of obtaining a hypertonic aqueous humor would be the production of bicarbonate in excess of that found in the plasma as a result of metabolism of the ciliary epithelium, a possibility consistent with recent experiments by Kinsey[15] who has shown that in the rabbit there is a relatively large excess of total CO_2 in the aqueous humor compared with that in the plasma, averaging, in 7 cases, 6.3 and 12.0

millimoles higher than the venous and arterial blood, respectively.

SUMMARY

The rate of flow of aqueous humor in rabbit eyes has been derived within narrow limits from the rate of disappearance from the anterior chamber of three test substances, para-aminohippuric acid, Rayopake, and Diodrast, and from the ratio of the concentration of these substances in the aqueous humor to that in the plasma water under steady-state conditions.

By assuming that all three test substances enter either by diffusion or secretion, respectively, the limits for rate of flow were found to be 1.07 to 1.30 percent of the volume of the anterior chamber per minute. From all of the evidence available the best value for rate of flow was considered to be 1.1 percent per minute which is equivalent to about 2.75 cubic mm. of aqueous humor per minute.

The average rate of disappearance of sodium was found to be 1.08 percent per minute, which corresponds almost precisely with the minimum rate of disappearance imposed by flow on all aqueous humor constituents not preferentially held back at the filtering angle of the eye. The ratio of the concentration of sodium in the anterior chamber to that in the plasma water at steady state was found to be 0.93. From these figures it was inferred that sodium must leave the anterior chamber almost entirely by flow and enter the anterior chamber predominantly by a unidirectional active process (secretion).*

The general relation between the steady-state distribution ratio aqueous humor/plasma and rate of disappearance for any nonmetabolized substance entering either by diffusion or secretion or both, was expressed graphically using the experimentally established value for the rate of flow. By reference to the graph, deductions can be made readily concerning the mode of entrance into

* See footnote page 189.

the anterior chamber for all substances whose steady-state ratios and rates of accumulation are known.

It was concluded that within the limits of error of the available data, sodium, chloride, thiocyanate, phosphate, and probably ascorbic acid enter the anterior chamber predominantly as a result of a secretory process and leave predominantly by flow; whereas, ethyl alcohol and urea enter predominantly by diffusion and leave both by flow and by diffusion.

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DISCUSSION

DR. DAVID G. COGAN (Boston, Massachusetts): Such an outstanding paper ought, I think, have some discussion. I am not the one to open it but in order for us to arrive at a simple general rule, I would like to ask Dr. Kinsey if it is correct to state that all substances which are ionized appear to be secreted while those which are not ionized seem to obey laws of diffusion. Moreover, has not much of the confusion in the past regarding the formation of the aqueous been due to the consideration of the aqueous humor as a whole rather than to its various constituents? Dr. Kinsey and Dr. Bárány have shown that there are at least two means by which substances enter the anterior chamber from the blood.

DR. JOHN E. HARRIS (Portland, Oregon): I would like to ask Dr. Kinsey whether his studies of the kinetics of entrance of the compounds, which his analyses show are secreted into the aqueous, have enabled him to determine the order of the reaction. We have been perplexed by this

problem. In the development of the mathematical expressions which we used in the analysis of our data, we pointed out that, where the movement in any one direction is considered to be by strict diffusion, the rate of the movement is proportional to the concentration. The proportionality constant is the "k" of our expressions and the "k_{diff}." of Dr. Kinsey's expressions. The kinetics of this type of movement will be that of a first-order reaction, and the k values calculated will be the same over the entire range of concentrations, all other things being equal.

On the other hand, if a substance moved by secretion it might be expected that the rate of movement would be proportional to the product of the concentration and some function of the cell. On the face of it, this is a second-order reaction, but the kinetics of the movement would depend upon the nature of the cellular function and would be difficult to predict.

If the limiting factor were the concentration of the substance to be secreted, the kinetics would be that of a first-order reaction and the movement would be proportional to the concentration. At the other extreme, where the limiting factor is the cellular function, the movement would be totally independent of the concentration. In any event, where the function of the cell is included in the calculated proportionality constant, as it is in Dr. Kinsey's "k_{secr}," one would expect that the k value as calculated would not be the same over a wide range of concentrations. Unfortunately, there are so many other variables in the in vivo, plasma-anterior chamber system, that it is difficult to establish this relationship, and I was wondering what luck Dr. Kinsey has had in its evaluation.

DR. KINSEY: Dr. Harris has raised an important question, and one which we have indeed considered in evaluating our "k" factors. In our experiments in which sodium

was the test ion it will be recalled that we used radioactive sodium. This method enables one to trace the passage of sodium from the blood to the aqueous humor without appreciably changing the concentration of sodium in the blood. In this way one avoids any limitation in transfer rate associated with cellular function.

In earlier work with ascorbic acid, I did encounter just the type of limiting factor of which Dr. Harris speaks. In this instance, when the concentration of ascorbic acid in the plasma exceeds 3 mg. percent, there appears to be no further increase in the rate of transfer of this compound into the anterior chamber (Kinsey, V. E: Transfer of ascorbic acid and related compounds across the blood-aqueous barrier. Am. J. Ophth., 30:1262, 1947).

I agree with Dr. Harris that the proportionality constant "k" for a substance which diffuses would not be influenced by the relative concentration in the plasma compared with that in the aqueous humor.

DR. KINSEY (closing) : I would like to thank Dr. Cogan for his kind remarks and say that as a simple rule our findings to date indicate that water and all nonelectrolytes appear to enter the anterior chamber of the eye by diffusion; whereas, the electrolytes enter the anterior chamber by an energetic process which we have defined as secretion.

I would agree with Dr. Cogan's statement that much of the confusion regarding the formation of aqueous humor has arisen from the consideration that the aqueous humor is formed as a whole. Further confusion arises too, I believe, from considering that aqueous humor is formed in but one place in the eye; whereas, our results indicate that nonelectrolytes and water enter the eye both from the iris and probably from the ciliary body. The electrolytes, on the other hand, enter the eye exclusively somewhere posterior to the iris, probably the ciliary body.

THE STEADY STATE OF CORNEAL HYDRATION*

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It is desirable to know the percentage of water present in the corneas of experimental animals since, in contrast to the relatively inert mass of stroma, water is the continuum in which most of the chemical reactions occur in this area. Furthermore as Fischer[1-4] has demonstrated, the transparency of the cornea varies with the water content. Krause[5] has warned that the percentage of corneal hydration obtained by experimental measurement varies with "age, species, and method of manipulation of the tissue."

There is little uniformity in the literature concerning the percentage hydration of either the cornea[6] or sclera.[7] This study was undertaken, therefore, to determine statistically the water content in the bovine, rabbit, and cat cornea and to compare the value with that found in the sclera of the same species. The results indicate that within a given species the water content of the cornea is an extremely constant value.

METHODS

Bovine eyes. The corneas and scleras were obtained from animals of both sexes varying from 1 to 6 years in age. The animals were killed by a bullet shot through the brain. The carotid arteries and jugular veins were then incised, and the animals were permitted to bleed to death.[†] The eyes were enucleated while the animals were still in the convulsions of extremis, and the corneas were dissected from the enucleated globe before the animals had actually expired. The corneas were dissected within a few seconds, employing a forceps and scissors and a minimum amount of manipulation. They were carefully blotted with fine-grade filter paper and were transferred to previously tared weighing bottles which were closed with greased glass stoppers. These bottles plus the contained samples were weighed within an hour of the time of enucleation, and the difference in weight represented the wet weight of the tissue. The grease was then removed from the ground-edge surfaces, and the open bottles and tissues were exposed to 115°C. for 48 hours. The bottles were then re-weighed with and without the tissue, the difference representing the dry weight.

The scleral samples were carefully dissected free from adnexa after both corneas had been removed. They were sealed and weighed in the same manner as described for the corneas.

No attempt was made to obtain total weights of the cornea or the sclera. All weights recorded herein are of representative samples of these two tissues. The weighings were made to the nearest 0.1 mg.

Rabbit. The same procedures were employed in the rabbit experiments except that these animals were killed by injecting 10 cc. of air intravenously.

Cat. The first series of cat eyes was removed from animals which had been subjected to ether anesthesia for periods of 1 to 3 hours. Another group of corneas was obtained from unanesthetized cats killed with intravenous air emboli. These latter corneas were removed from the eye in situ after death. The same weighing procedure was followed as described above for the other species. In the experiments on rabbits and cats middle-aged animals of both sexes were used.

RESULTS

The data are summarized in Table 1. From the table it can be seen that corneal hydration of a given species does not vary to a great extent from animal to animal. In

<div align="center">TABLE 1</div>

<div align="center">CORNEAL AND SCLERAL HYDRATION IN EXPERIMENTAL ANIMALS</div>

Species	Cornea			Sclera		
	No.	% Hydration	S.D.	No.	% Hydration	S.D.
Bovine	25	77.77	0.63	25	68.07	1.90
Rabbit	25	77.67	1.15	25	68.30	2.81
Cat—etherized	38	75.39	1.73	37	67.69	4.92
air-injection	27	76.40	1.62	—	—	—

all instances the standard deviation for the corneal tissue is less than one half of that for the sclera.

DISCUSSION

It is difficult to obtain reliable samples of sclera because of the closely bound chorioid and ciliary body on one side and episclera and inserting muscle tendons on the other. Furthermore, the peculiar anatomy of the ciliary body in the carnivora[8] precludes the possibility of obtaining uniform specimens of the sclera from random sampling of the available sclera. This may account for the relatively high standard deviation in the hydration of cat sclera as shown in Table 1.

In a given species the mean corneal hydration is an extremely constant value from a biologic point of view. This suggests that there is some controlling mechanism operating to keep the water content at a constant level.

Cogan and Kinsey[9] showed that the semi-permeable membranes on the anterior and posterior surfaces of the cornea maintain a constant circulation through this region and keep the tissue in a "dehydrated state." This terminology may be confusing unless one appreciates that the "dehydration" is expressed in terms of possible hydration. In

<div align="center">TABLE 2</div>

<div align="center">CORNEAL AND SCLERAL HYDRATION (BOVINE EYES)</div>

Cornea Wet Wt. (mg.)	Cornea Dry Wt. (mg.)	Cornea % H_2O	Sclera Wet Wt. (mg.)	Sclera Dry Wt. (mg.)	Sclera % H_2O
401.4	90.0	77.6	26.6	9.6	63.9
373.1	87.0	76.7	22.7	8.4	64.0
378.6	85.1	77.6	42.8	15.1	64.6
358.8	81.5	77.3	65.4	21.2	67.5
389.6	88.3	77.3	103.6	32.1	68.4
407.7	91.3	77.6	151.1	44.6	70.6
610.8	109.2	82.1	283.6	88.5	69.2
462.6	101.3	78.0	175.4	52.6	70.0
427.5	92.6	78.4	282.5	90.6	68.0
443.5	95.0	78.6	209.0	64.0	69.4
428.2	90.7	78.8	397.8	115.0	71.0
441.4	93.1	78.9	226.5	70.6	69.8
520.6	112.9	78.3	172.8	59.0	65.9
528.4	115.4	78.1	273.2	86.9	68.2
443.3	102.0	77.0	198.5	63.7	67.9
432.5	97.1	77.5	95.5	30.9	67.6
446.9	104.3	76.9	256.1	82.8	67.8
494.4	113.4	77.0	220.8	70.3	68.2
381.2	83.5	78.1	155.1	47.3	69.6
368.1	83.2	77.4	162.4	53.5	68.1
497.6	108.9	77.1	304.1	93.5	69.4
498.1	109.0	77.3	274.7	88.3	67.9
538.4	118.6	78.0	736.3	230.9	68.6
595.6	127.6	78.6	762.8	227.6	70.1
473.5	106.5	77.5	441.2	149.4	66.1
Mean		77.77			68.07
S.D.		0.63			1.90

TABLE 3

CORNEAL AND SCLERAL HYDRATION (RABBIT EYES)

Cornea Wet Wt. (mg.)	Cornea Dry Wt. (mg.)	Cornea % H₂O	Sclera Wet Wt. (mg.)	Sclera Dry Wt. (mg.)	Sclera % H₂O
70.1	16.2	76.9	40.1	14.4	64.2
71.4	16.1	77.2	64.9	20.6	68.2
76.2	16.7	78.2	44.0	14.8	66.4
82.2	17.1	79.2	45.5	14.1	69.0
63.7	13.4	78.9	36.5	13.8	61.2
57.9	12.6	78.2	41.5	14.0	66.3
64.5	16.1	75.0	51.5	19.6	62.0
66.7	15.8	76.3	46.6	15.8	66.1
86.5	18.8	78.3	59.6	20.4	65.8
84.6	19.1	77.4	62.9	20.6	67.2
100.1	22.7	77.4	79.7	24.5	69.2
104.9	23.1	78.0	57.6	19.0	67.0
88.8	19.2	78.4	34.0	9.1	73.3
85.5	18.4	78.4	48.1	15.1	68.4
72.2	16.0	77.8	45.0	12.4	72.4
70.6	16.4	76.8	62.1	19.2	69.0
59.9	14.1	76.5	39.6	12.5	68.4
57.4	13.8	75.9	63.5	19.0	70.0
69.0	16.6	75.9	64.5	17.5	72.9
76.0	17.0	77.6	60.8	20.0	67.1
77.1	17.1	77.8	63.7	16.0	73.6
76.6	17.0	77.8	68.5	22.2	67.6
81.0	16.4	79.7	84.1	22.3	73.5
95.0	20.0	79.0	123.2	38.7	68.6
107.0	22.4	79.1	120.6	36.0	70.2
Mean		77.67			68.30
S.D.		1.15			2.81

TABLE 4

CORNEAL AND SCLERAL HYDRATION (CAT EYES (ETHERIZED))

Cornea Wet Wt. (mg.)	Cornea Dry Wt. (mg.)	Cornea % H₂O	Sclera Wet Wt. (mg.)	Sclera Dry Wt. (mg.)	Sclera % H₂O
173.9	46.6	73.2	49.4	17.5	64.6
179.6	48.0	73.3	33.2	13.5	59.4
152.9	45.7	70.1	25.0	11.4	54.5
169.7	46.9	72.4	24.9	8.7	65.0
216.0	53.3	75.4	42.0	14.3	66.0
225.8	55.6	75.4	54.0	16.5	68.4
151.5	39.3	74.1	61.4	17.9	70.9
173.9	41.6	76.0	76.8	20.3	73.5
159.6	36.6	76.3	70.9	20.8	70.7
159.0	36.0	77.4	60.4	18.0	70.1
186.0	44.6	76.0	77.6	18.6	76.0
180.2	42.3	76.6	47.4	17.2	63.6
121.9	29.8	75.6			
125.9	31.0	76.0	48.5	16.0	67.0
141.2	31.5	77.7	34.3	10.0	70.8
135.1	30.8	77.3	35.5	11.0	69.0
98.6	20.6	79.1	22.2	6.5	70.5
91.6	20.0	78.2	16.7	5.3	68.2
140.0	32.6	76.6	92.5	24.1	73.9
137.3	33.2	75.7	50.4	13.2	73.8
118.7	28.0	76.4	25.2	9.9	60.6
123.4	27.8	76.6	33.6	12.2	63.8
130.4	30.7	76.6	51.0	16.4	67.9
125.5	32.4	74.2	17.9	7.2	59.8
86.8	21.4	75.0	51.5	15.7	69.5
91.1	20.3	72.7	34.7	12.0	65.4
Mean		75.39			67.69
S.D.		1.73			4.92

TABLE 5
Corneal hydration (cat eyes (air emboli))

Cornea Wet Wt. (mg.)	Cornea Dry Wt. (mg.)	Cornea % H_2O
68.7	14.6	78.8
72.9	18.1	75.2
73.3	15.9	78.3
176.7	41.7	76.3
206.1	48.8	76.4
157.3	36.9	76.6
177.9	42.5	76.1
164.5	40.5	75.4
167.7	33.4	80.0
174.1	41.1	76.5
152.3	39.6	74.1
171.6	36.5	78.7
152.8	38.2	75.0
153.2	38.0	75.3
169.2	37.4	77.9
195.6	48.5	75.3
170.3	44.4	74.0
211.8	48.0	77.3
190.0	46.0	75.8
164.9	37.5	77.8
210.6	50.4	76.1
183.8	49.6	73.0
181.8	42.7	76.5
198.4	45.1	77.3
232.1	48.6	78.1
218.2	53.2	75.7

Mean		76.40
S.D.		1.62

other words the cornea can swell to 300 to 400 percent of normal and the reason that this does not occur normally is because of the dehydration action of the semipermeable membranes. The present investigation supports Cogan and Kinsey's theory.

It is possible that these membranes act as governing mechanisms to control the maintenance of a very constant water content. This assures a normal transparency and uniform milieu in the tissue. Most of the changes which occur in the cornea following trauma to either surface are perhaps primarily due to the absence of these controls.

This explanation of corneal opacification has been partially postulated by Kronfeld[10]

and others but experimental substantiation has been lacking.

That the matter may be much more complex is indicated by the recent work of Hart[11, 12] who shows that many factors besides water content affect the transparency of the cornea and must be considered in any theory of normal corneal transparency.

There is a difference between the corneal hydration of the etherized and air-injected cats in this experiment. The dehydration which occurs in the living eye when the lids are open for a prolonged interval alters the data significantly. It is likely that even greater errors would occur if the enucleated eye or excised cornea were permitted to dehydrate. The tissues must be fresh to yield reliable data. The lack of information regarding these facts may account for some of the discrepancies which are recorded in the literature.[6, 7] Although the age extremes were not included in the study, it was observed that there is no variation in corneal hydration within the age spans investigated, nor was any variation found with the sex of the animals.

Finally the simplicity of the techniques involved in the determination of corneal and scleral hydration suggests that this study would be a suitable laboratory exercise for courses in basic ophthalmology.[13]

Summary and Conclusions

The corneal and scleral hydration of bovine, rabbit, and cat eyes has been determined and has been statistically analyzed. The uniformity of the corneal data as compared with the scleral data is interpreted as an indication of the controlling forces which are exerted by the corneal semipermeable membranes.

Medical Laboratories.

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DISCUSSION

DR. DAVID G. COGAN (Boston, Massachusetts): Dr. Duane has carefully chosen fresh specimens to determine the water content of normal cornea. This is of the utmost importance for a cornea will spontaneously imbibe water during the first few hours after enucleation and, if the specimen is not fresh, one obtains an abnormally high water content. Presumably the permeability of the endothelium is altered or the stromal fluid becomes more hypertonic through evaporation from the surface so there is no longer an osmotic gradient and semipermeable membrane separating the stroma from the aqueous.

The purpose of a maintained dehydrated state is presumably transparency. If the cornea is allowed to swell, it may become as opaque as the sclera and, on the other hand, if the sclera becomes dehydrated to an extent comparable to that of the normal cornea, it becomes transparent, but it is important to remember that turgescence should always be recorded as a function of the imbibitory power of the tissue and not of its absolute water content.

DR. DUANE (closing): I would like to thank Dr. Cogan for his remarks. I perhaps did overstress the fact of transparency factors when discussing the constancy of the corneal hydration. Of course, a great many other functions can be ascribed to the cornea and perhaps many just as important as the transparency effect.

We all know that the enzymes present in the epithelium layer and endothelium layer and possibly other mediums which are present in the stroma, such mediators as were suggested by Dr. Friedenwald in his talk this morning, all of those constituents require a rather constant environment for their optimal action and if the environment changes to any appreciable extent one way or another, these enzymes are not able to function as normally as they would under optimal conditions.

I am not exactly certain. We haven't investigated the fact of how much trauma or change in the semipermeable membranes in the epithelium and endothelium is required to produce a change in the transparency of the cornea.

I think that that might be an experiment which could at least be looked into. As I conceive it, slight metabolic changes of either of these layers produce what we recognize plainly, at least in the very early stages, with a slitlamp as an opacity. Bedewing of the various layers or slight opacity formation (transient opacities such as striate keratitis) might be ascribed to the loss of the protecting action of the two layers. I think it is quite likely that these opacities occur because of an inhibition of the protecting action of the semipermeable membranes or at least the metabolic enzymes and other controlling factors which are acting in those regions.

THE USE OF ISOLATED RETINAL TISSUE IN STUDIES OF THE METABOLISM OF THE CENTRAL NERVOUS SYSTEM*

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Cellular respiration processes are extremely important for both the functioning and survival of the cerebral cortex and the retina and, if the supply of either oxygen or substrate is interrupted, unconsciousness follows quickly. Manometric studies on the metabolism of isolated brain have revealed something of the nature of the enzyme systems that are involved in oxidation, and of the effects of anesthetics and other pharmacologic agents. A comparison of the metabolism of the cerebral cortex and the retina may be of interest to the ophthalmologist because of interest both in the retina itself and in the information that retinal studies may give about the physiology of the central nervous system.

Physiologically, the retina resembles cerebral cortex in its high rate of oxygen consumption, its unusually high rate of both aerobic and anaerobic glycolysis,[1] its dependence upon glucose substrate, and the almost complete depression of respiration produced by heavy metal inhibitors.[2] Since the retina is derived from neuroectoderm, a morphologic similarity is to be expected, and this has been shown to be true up to the 45-mm. stage of embryologic development.[3] In the adult tissues, in spite of specialization of each, a similarity remains in the lamellar arrangement of nerve cells, synaptic, and nerve-fiber layers.

Isolated rat retina is a convenient tissue for use in manometric metabolism measurements. It is easily and quickly removed from the eye with relatively slight injury, and is thin enough to permit adequate oxygenation without slicing, even though air is the gas phase rather than 100-percent oxygen.

If the suspension medium is buffered and contains glucose and a properly balanced salt mixture, linear respiration may be obtained for a period of 5 to 7 hours. It is thus possible and convenient to measure respiration during a control, experimental, and recovery period on the same tissue. Since the rat retina does not break up while it is shaking in the manometer, it may be easily removed and weighed at the end of the experiment.

Experimental determination of respiration in isolated brain is complicated by the procedure of cutting thin slices of the tissue in order to insure adequate oxygenation. Since the nerve cells are extensively branched, it is evident that a slice of optimum thinness must have a high proportion of cells with cut processes. It is recognized that cutting a nerve process may cause degeneration of the cell body even though the cell is otherwise undisturbed. In an artificially prepared saline solution, there may be additional injury from diffusion into the cell of ions in a concentration different from the normal constitution. Certain experimental agents that do not penetrate the intact cell may likewise adversely and misleadingly affect the brain slice. The necessity for use of 100-percent oxygen also complicates certain determinations because of the oxygen-poisoning effect.

TECHNIQUE

The experiments described in the present paper were performed on albino rats. The animals were killed by breaking the neck, and either the eyes or the brain was removed immediately. In studies on cerebral cortex, the brain was sliced by means of a razor blade and a transparent plastic template.[4] The slices were weighed on a microtorsion balance before they were immersed in physi-

ologic saline solution. Retinas were removed by cutting around the globe just posterior to the ora serrata. The retinas were then lifted out and cut into halves to prevent folding.

The isolated tissues were suspended in phosphate-buffered saline solution at pH 7.35 containing 0.2-percent glucose.[5] Small Warburg manometer flasks containing a total volume of about 7 cc. were used for the oxygen consumption determinations. The center wells contained 10-percent KOH on filter paper. Temperature of the water bath was 37.2°C. Unless otherwise mentioned, experiments on retinas were performed with air as the gas phase and those on brain slices with 100-percent oxygen.

Retinal weights were determined after rinsing the tissues at the end of the experimental periods and drying them on weighed cover glasses at 110°C. The dry weights for the brain slices were calculated from the recorded wet weights by means of a wet-dry ratio obtained by drying sample tissue at 110°C.

In the histologic studies, brain tissue was prepared in the following manner: For the control sections, Figure 5 (left), the brain was removed immediately after the death of the animal, and slices of the cerebral cortex were cut and placed in 10-percent neutral formalin for fixation.

In other specimens studied, slices of tissue were placed in manometer flasks in the phosphate-glucose-saline solution. These flasks were then placed in the water bath and the respiration rate was recorded for one-half and 2½-hour intervals in order to verify the viability of the tissue. Following this, the tissue was removed from the flask and fixed. A similar procedure was used in experiments on the rat retina.

In addition, tissue slices and blocks from rat brain were stored in saline solution at 4°C. for intervals varying from 2 to 24 hours. At the end of the storage period, the brain tissue was placed in formalin for fixa-

tion. Sections made from all preparations were stained with hematoxylin and eosin.

EXPERIMENTAL RESULTS AND DISCUSSION

Results of a number of experiments seem to indicate that in the tissues studied oxygen consumption is not dependent upon the integrity of the cell. Both cortex slices or chopped tissue made by cutting the cortex into small pieces respire at about the same level. Similarly, either intact retina or retina which has been cut into small pieces shows the same oxygen uptake for a period of at least one hour. However, if the tissues are ground up in a tissue grinder, then the respiration falls off considerably. It is possible that as long as the gross intracellular organization is not appreciably disturbed, the respiratory enzyme systems may function at a normal rate.

Figure 1 shows that when a properly buffered and balanced saline solution containing glucose is used, the respiration of the retina in air is maintained at a constant rate for as long as 7 hours. The lower curve in the figure shows the course of oxygen consumption when a retina is run in fluid containing no glucose. The rapid decline in respiration to almost the zero level is convincing evidence that the process being measured in the respirometers is glucose metabolism rather than any sort of autolytic degenerative change.

There is a pronounced difference in the course of oxygen consumption of the retina in air and in 100-percent oxygen. In air, the rate of respiration is constant during the observation period. In oxygen, the rate of respiration is higher at the start of the measurement period, but there is a marked falling off and, by the time the experiment has been run for a period of 7 hours, the oxygen consumption has decreased to 50 percent of that of the specimen in air. This is shown in Figure 1.

The curve for brain respiration is similar to that for retina in oxygen and it may be

that if it were possible to run cortex slices in air, the respiration would be more constant. This is not feasible since a tissue slice that is thin enough to permit adequate oxygenation at the center, with air as the gas phase, is almost impossible to prepare.

The steady rate of respiration of the retina in air perhaps more nearly resembles the situation in the living animal, since the oxygen tension within the eye can certainly

tex slices, the response of the injured cells to certain chemical factors may be considerably different than would be expected from normal tissue. It is well known that highly dissociated acids do not go through the normal cell membrane.

Figure 2 shows the results of an experiment with brain slices and retinas in which the tissues were exposed to a saline solution at pH 5.2 for a period of one hour, after
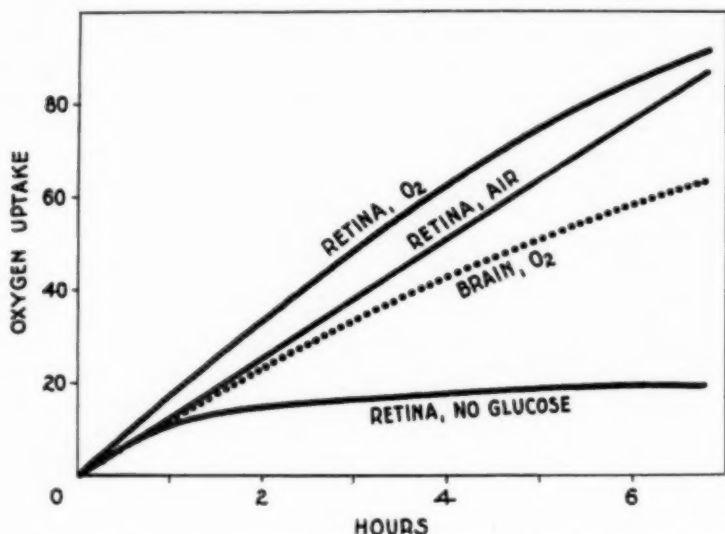
Fig. 1 (Robbie and Leinfelder). Oxygen consumption of isolated rat retinas in phosphate-buffered saline solution containing 0.2 percent glucose. Ordinate shows the mm.^{2} of O_2 consumed per mg. dry weight, and the abscissa the time in hours.

never approach that which exists in the flasks gassed with 100-percent oxygen. Whether the increase in oxygen consumption of the retina in oxygen at the start of the measurement period is actual respiration or simply oxidation of substrates that might not otherwise be utilized, is a question. The falling off in respiration at the end of the 6- or 7-hour period of measurement may possibly be an oxygen-poisoning effect.

Although the rate of respiration is perhaps not immediately affected by cutting the processes of the nerve cells in cerebral cor-

which the recovery oxygen consumption was measured. Although the retina has apparently not been damaged by this exposure to an acid environment, the cortex slices with their cut cells and processes show considerable injury, as evidenced by a marked decline in respiration. Kidney and liver slices also have been shown to recover almost completely after an hour's exposure to a medium at pH 5.[6]

Figure 3 shows the results of an experiment using 0.1M potassium chloride in the suspension fluid. In vivo, the potassium ion

penetrates the brain very slowly.[7] Yet the respiration of the brain slices is increased by almost 100 percent when a high concentration of potassium is included in the saline solution. (The sodium chloride concentration in these experiments was reduced to maintain an isotonic medium.)

The retina, on the other hand, shows, if anything, a slight decrease in oxygen consumption in the medium containing high potassium. Similar observations have been reported by Dickens.[5] This again indicates that potassium, whatever may be the nature of its stimulating action, apparently does get into the cortex cells which have been cut, but not into the retina cells.

The cytologic picture also gives evidence that the brain is much more injured during
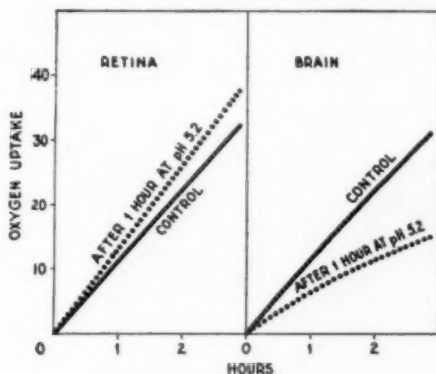
Fig. 2 (Robbie and Leinfelder). Recovery of retinas and cerebral cortex slices after one hour at pH 5.2. During the exposure period the tissues were shaken in manometer flasks in glucose-saline solution containing 0.01M. primary sodium phosphate. Ordinate shows oxygen uptake during recovery period in mm.[3] O_2 per mg. dry weight.

preparation for respiration measurement than the retina. Figure 4 shows sections from a control retina and one which had been run for $2\frac{1}{2}$ hours in a manometer flask at 37.2°C. The ganglion cells and the other retinal cellular elements were similar in both the control and in the experimental tissues at the end of the experiment.

With brain tissue, on the other hand (fig. 5), edema was noted after one-half hour in the Warburg flasks, and the ganglion cells had begun to undergo chromatolytic change, as shown by the swelling of the
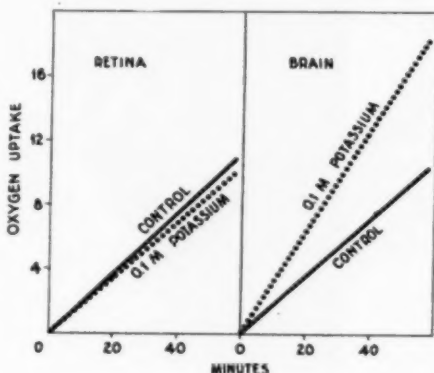
Fig. 3 (Robbie and Leinfelder). Effect of addition of 0.1M. KCl to phosphate-buffered saline solution on the respiration of retina and cerebral cortex slice. Ordinate: mm.[3] of O_2 per mg. dry weight.

cytoplasm and nuclei. In some instances, the ganglion cell nuclei were extremely vacuolated, indicating karyorrhexis. These changes were considerably exaggerated in a $2\frac{1}{2}$-hour specimen and many of the ganglion cells had disappeared, while all of those remaining showed advanced chromatolysis. In some instances, glial clumping about the ganglion cells could be observed. A similar type of change was observed after two hours' storage at 4°C, and this became increasingly apparent after longer storage periods.

When the brain remains intact in the dead animal at room temperature for as long as $2\frac{1}{2}$ hours, chromatolytic changes do not occur. However, if the brain is removed and tissue slices or blocks are prepared, evidence of cellular damage can be recognized within half an hour if the tissue is maintained at 37°C.; similar changes are apparent after two hours when the tissue is kept at 4°C. After greater periods of time, more severe
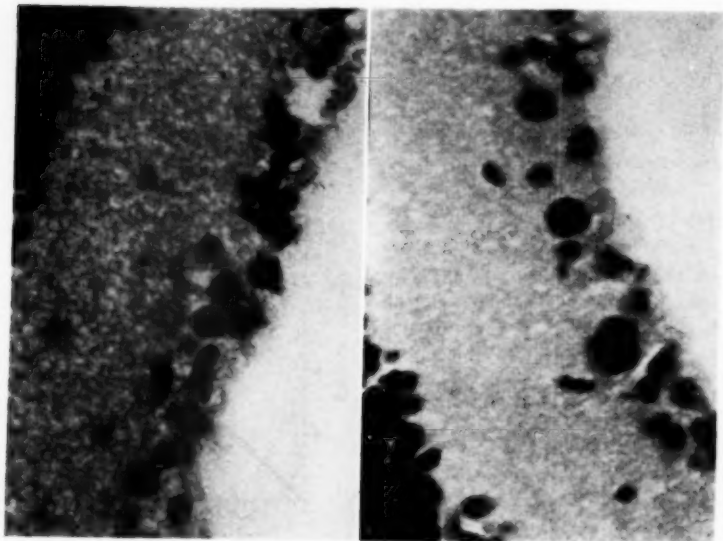
Fig. 4 (Robbie and Leinfelder). Photomicrographs of sections of rat retinas. (Left) Control section. (Right) Section of retina shaken for 2½ hours in manometer flask at 37.2°C.
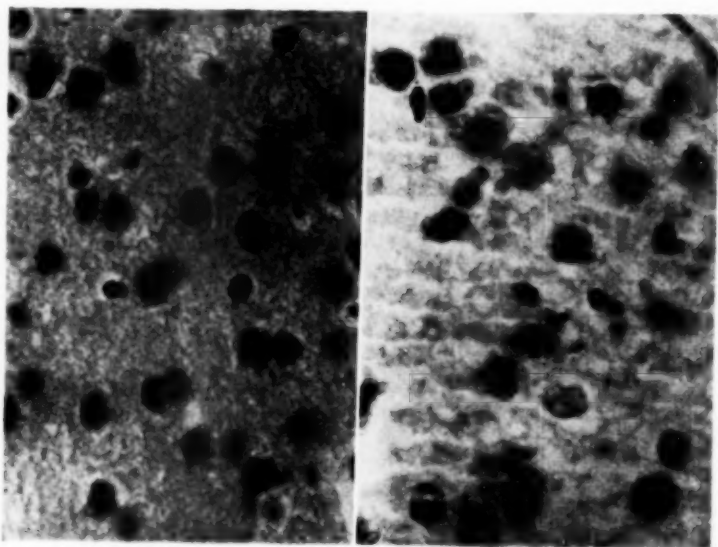
Fig. 5 (Robbie and Leinfelder). Sections of rat cerebral cortex slices. Control on left fixed immediately after death. Experimental tissue on right shaken for one-half hour in manometer flask before fixation.

chromatolytic phenomena are apparent.

These changes, which are identical with those occurring in encephalomalacia, appear to be the result of injury to the ganglion cells or their processes, and the chromatolytic response may occur directly as a result of the injury to the cells or indirectly because of the change in the intracellular chemical environment that occurs when the cut cells are placed in physiologic saline solution. (The concentrations of certain ions in protoplasm are quite different than those in blood plasma.)

In the preparation of retinal tissue, the ganglion cells themselves are not directly injured and only the axone is cut. This injury to the retinal ganglion cell axone occurs at some distance from the cell body, and is less severe trauma than that which occurs to the ganglion cells of the brain when tissue slices are prepared, for, in the latter case, both cell processes and the cells themselves are cut. With the brain slices, a much greater proportion of the cell cytoplasm is exposed to an abnormal chemical environment than in the retina when the main mass of the tissue has not been disrupted.

CONCLUSIONS

The structural and physiologic similarity between the cerebral cortex and the retina make it seem probable that the respiratory response of the retina is, in many ways, truly indicative of central nervous system metabolism. Rat retinas are convenient to prepare and to use in manometric determinations, and the period of constant oxygen uptake is long enough to allow measurement of experimental treatment periods and recovery in the same tissue.

Injury to the cell membrane in cerebral cortex slices is evidenced by hydrogen ion effect and potassium stimulation of respiration, as well as by a rapid cytologic response to the injury. In studies involving an agent that normally does not penetrate the brain cell, results may be more representative if measurements are made on the retina rather than on a brain slice.

The toxic action of pure oxygen on the retina, and the similarity of the curves representing respiration in oxygen of the retina and the brain, also indicate that brain metabolism in 100-percent oxygen is probably not normal.

It is believed that studies of the retina may in some ways be more clearly indicative of central nervous-system metabolism than observations on brain slices, and it may be advisable to use the retina for comparison and control experiments.

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DISCUSSION

DR. T. D. DUANE (Iowa City, Iowa):
Granit in Sweden, Adrian in England,
Bronk, Hartline in the United States have
shown that the retina is an ideal tissue upon
which to study electrical phenomena in
the body, action potential currents, second-
ary to stimulation, and so forth.

Dr. Robbie has just pointed out that the
retina is an ideal tissue upon which to study
metabolic activities of the central nervous
system. It seems to me this is a typical exam-
ple of the point which Dr. Friedenwald was
making last night, that we are opening new
vistas in research in ophthalmology, be-
cause the next obvious step is to make a
correlation between electrical phenomena
and metabolic phenomena.

In other words, it seems conceivable to
me that one might injure the various por-
tions of the retina, say the rods and cones,
bipolars, or the ganglion cells, to see what
effect that has upon the electrical phenom-
ena in the electroretinogram, and then the
retina could be removed and studied in vitro
from the metabolic standpoint and I think
some very interesting correlation might be
made.

DR. P. J. LEINFELDER (Iowa City, Iowa):
The portion of this paper that has been par-
ticularly interesting and spectacular to me
is the portion dealing with the pathology in
the nervous system. Unfortunately, the lan-
tern slides do not show the great degree of
chromatolysis that occurs in the ganglion
cells of the brain.

You who have taken photomicrographs of
brain tissue at 800 or 900 magnification
know how difficult it is to show representa-
tive areas in a particular slide. However, the
effects of slicing the brain tissue are real
and occur with great rapidity for they can
be clearly recognized one-half hour after
sectioning. The paradox of the situation is
this.

If we leave the brain intact in the ani-
mal for 2, 4, 6 hours, and then remove the cal-

varium, take out the brain, take a thin slice
of it, and put it in fixative immediately, we
obtain perfectly normal histologic appear-
ances. However, if the brain tissue is sliced
and then allowed to lie in saline buffer solu-
tion with glucose and oxygen available, the
changes of chromatolysis take place. Such
changes are not recognized in the retina up
to 6 hours when the temperature is 37.5°C.,
nor up to 24 hours when the retinas are kept
at 4°C.

The occurrence of these chromatolytic
changes in nerve tissue which is assumed
to be dead is a particularly interesting prob-
lem and one which has to be investigated in
the light of what is taking place in the tis-
sues as far as respiration, glycolysis, and
utilization of substrate is concerned.

DR. DAVID G. COGAN (Boston, Massachu-
setts): I would like to ask Dr. Robbie if
there is any contradiction in the apparent
susceptibility of the retina to anoxemia, as
judged by "black-outs," and the apparent
resistance of the retina to oxygen lack as
determined by studies in the Warburg ap-
paratus.

DR. ROBBIE (closing): I would like to say
that I have no way of knowing what effect
the proteolytic enzymes may have on the
histologic structure of the tissue. To Dr.
Cogan's comment I may say that I think
the two factors are possibly quite dissociable
—oxygen consumption and the preservation
of the visual functions. It is well known of
course that the anoxic retina loses its power
of perceiving light very rapidly, and anoxia
for a period of 7 minutes in the intact eye
leads to permanent blindness. Yet if we kill
the animals and keep the dead bodies at
37°C. for a period of 45 minutes and then
take the retinas out and measure them in
the manometer flasks, the oxygen consump-
tion is apparently normal. So it seems as if
the limiting element in the system is some-
thing other than a chain of respiratory
enzymes.

It may be that the ganglion cells themselves are particularly susceptible in some way morphologically or chemically.

To Dr. Duane's contribution, I would like to discourse somewhat on his use of the word "ideal." We do not believe that the retina is necessarily ideal for these purposes. For example, Dr. Friedenwald suggested to me that perhaps the pigment layer is important in retinal function. When we take the retina out of the eye and leave the pigment layer behind, we no longer have a completely normal retina, and perhaps we are disturbing the function in that way. Furthermore, when an animal is killed, unless the eye is fixed immediately, the rod and cone layer quickly becomes diffused in appearance. So the retinas we are studying probably do not have an intact rod and cone layer. What we are measuring is the metabolism of the surviving cells. Any conclusions regarding vision that involve the photochemistry of visual purple are perhaps not shown by these studies. The one point that I do wish to make is that possibly the retina is more representative of the normal central nervous system than the cerebral cortex slice, and at least it may be valuable to compare both types of tissues when the effect of a drug is being studied so that it may be possible to evaluate the factors of permeability and injury.

METABOLISM OF THE CRYSTALLINE LENS*

I. WATER CONTENT AND GROWTH RATE

LAWRENCE O. ELY, M.D.
Iowa City, Iowa

Water is quantitatively the major constituent found in the crystalline lens. Accurate interpretation of certain lenticular properties, namely, QO_2, is dependent upon a precise knowledge of the ratio of wet weight to dry weight. Bellows[1] presents a table summarizing the information in the literature concerning the water content of bovine lenses (Table 1), but it is of note that the cases cited by any one worker are too few in number to be of statistical significance except for Salit's[2] figure of 65.41-percent water for 1- to 4-year-old bovine lenses. However, Krause[3] gives a statistically reliable water content of 67 percent in 1-year-old bovine lenses, but he gives no indication of the changes occurring with growth.

Salit[2] found the water content of the rabbit lens to be 59.25 percent (the mean of only two cases), while Brückner[4] reports the water content as 62.7 percent (also the mean of two cases). No report on the age of the animals was made by either worker. Field and others[5] found a mean dry weight of 30.7 percent, which would indicate a water content of 69.3 percent.

Brückner[4] reported the water content of a lens from a 5-day-old cat as 74.5 percent. No other references on the water content of cat lenses have been found in the literature.

Therefore, it is important to make a more extensive study of the water content of the crystalline lens to correlate its relationship with the age of the animal in cattle, rabbits, and cats, three species commonly employed in experimental studies of the eye.

METHODS

The eyes were removed from the animals within a few minutes of their death.[†] All

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† The cattle eyes were obtained through the courtesy of Gay's Locker Plant, Iowa City, Iowa, and Wilson Packing Company, Cedar Rapids, Iowa.

TABLE 1

WATER IN BOVINE LENSES

Age (years)	Number of Lenses	Author	Percent Water	Percent Water (weighted average)
1	6	Cahane	60.17	
	18	Bürger & Schlomka	68.70	66.70
	6	Jess	66.27	
	4	Salit	67.94	
1–4	49	Salit	65.41	
	10	Bürger & Schlomka	65.60	64.9
	16	Jess	64.65	
	6	Cahane	59.81	
5–9	12	Jess	63.99	64.4
	11	Bürger & Schlomka	64.9	
10–14	10	Jess	63.2	63.7
	10	Bürger & Schlomka	64.2	
15–17	8	Bürger & Schlomka	63.4	63.5
	2	Jess	63.82	
Unknown	?	Simon	65.76	
	4	Laptschinsky	63.51	

TABLE 2

RELATIONSHIP OF THE AGE OF BEEF TO THE TOTAL WEIGHT AND WATER CONTENT OF THE CRYSTALLINE LENS

Age (years)	No. of Lenses	Weight in Grams			Percent Water		Standard Deviation*
		Range (wet)	Mean (wet)	Mean (dry)	Range	Mean	
0–1	42	0.9036–1.4641	1.1781	0.3783	66.53–71.0	68.63	0.97
1–2	38	1.1878–1.7521	1.5984	0.5515	63.5 –68.1	65.6	1.24
3–4	32	1.6431–2.2417	1.9532	0.6991	61.9 –66.5	64.4	1.25
5–10	28	1.9645–2.7650	2.3042	0.8377	59.4 –65.0	63.7	1.56

* Standard deviation has been calculated from the formula, $\sigma = \sqrt{\dfrac{\Sigma x^2}{N}}$

x = the deviation of individual cases from the mean.
N = total number of cases.

TABLE 3

RELATIONSHIP OF THE AGE OF RABBITS TO THE TOTAL WEIGHT AND WATER CONTENT OF THE CRYSTALLINE LENS

Age (weeks)	Animal	No. of Lenses	Weight in Grams			Percent Water		Standard Deviation
			Range (wet)	Mean (wet)	Mean (dry)	Range	Mean	
1–4	A*	18	0.1769–0.3621	0.2529	0.0800	67.2–70.3	68.7	1.1
	P†	12	0.2001–0.4136	0.2981	0.0975	68.3–70.1	69.0	1.96
8–16	A*	28	0.5187–0.6600	0.5899	0.2042	62.9–67.1	65.4	1.03
	P†	4	0.6347–0.6648	0.6465	0.2180	65.7–67.2	66.4	—
20–36	A*	10	0.5942–0.6723	0.6196	0.2250	62.8–64.5	63.7	0.6
38–46	A*	12	0.5985–0.6723	0.6341	0.2345	60.7–64.8	63.1	1.56

* A—albino rabbits.
† P—pigmented rabbits.

TABLE 4

RELATIONSHIP OF THE AGE OF CATS TO THE TOTAL WEIGHT AND WATER
CONTENT OF THE CRYSTALLINE LENS

Age (months)	No. of Lenses	Weight of Grams			Percent Water		Standard Deviation
		Range (wet)	Mean (wet)	Mean (dry)	Range	Mean	
2–4	22	0.2896–0.3946	0.3533	0.1153	65.6–68.6	67.2	0.88
5–12	24	0.4983–0.6214	0.5457	0.1939	62.3–65.8	64.6	0.95
13–24	32	0.6175–0.7582	0.6745	0.2556	59.5–63.9	62.2	1.28
25 and over	24	0.7048–0.7943	0.7371	0.2835	59.5–63.2	61.6	1.16

lenses were dissected from the eyes within a short time after death of the animal, and in no cases did this time exceed one hour. The lens was removed intracapsularly in the following manner.

all cut, special care being taken to avoid rupturing the capsule. As the lens was gently eased out of the patellar fossa, the ligamentum hyaloideocapsulare was cut if the vitreous was adherent to the posterior capsule.
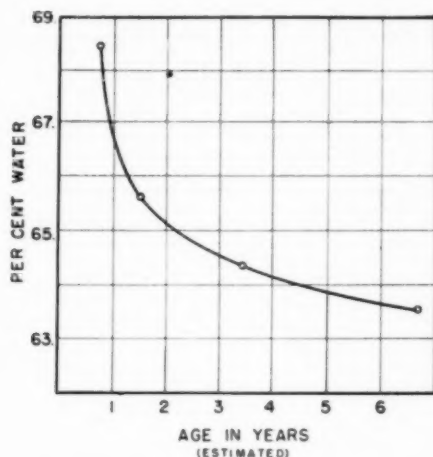
Fig. 1 (Ely). Relationship of age to water content of bovine lens.
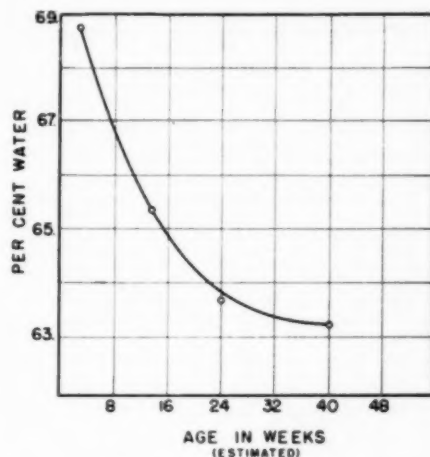
Fig. 2 (Ely). Relationship of age to water content of rabbit lens.

The cornea was removed and a total iridectomy was performed in order to expose the anterior surface of the lens and make visible the zonular fibers. These fibers were

After removal of the lens any adherent bits of vitreous were removed with forceps and scissors.

Each lens was weighed on a chainomatic balance and dried in an electric oven at 104°C. for 48 to 72 hours, or until the weight of the dry residue became constant on two successive weighings.

In these procedures two precautions should be noted: (1) The lens contains a certain proportion of water that is difficult

to remove by drying. Only by drying for 48 to 72 hours, or until the dry weight is constant, can this error be avoided. (2) The weight was noticed sometimes if the dried lenses were allowed to stand exposed to the air for several hours before weighing.
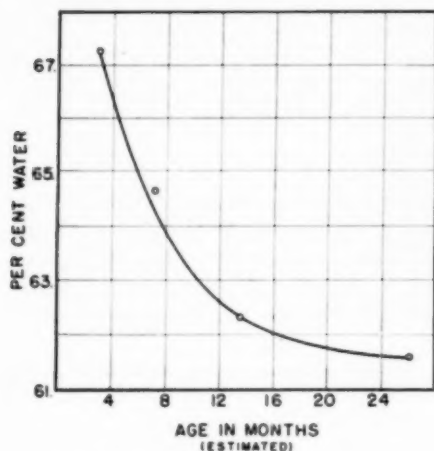
Fig. 3 (Ely). Relationship of age to water content of cat lens.
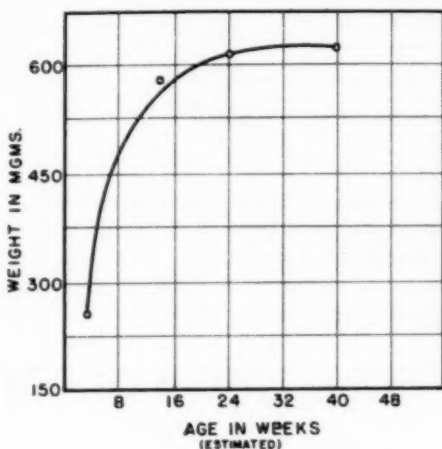
Fig. 5 (Ely). Growth rate of rabbit lens.
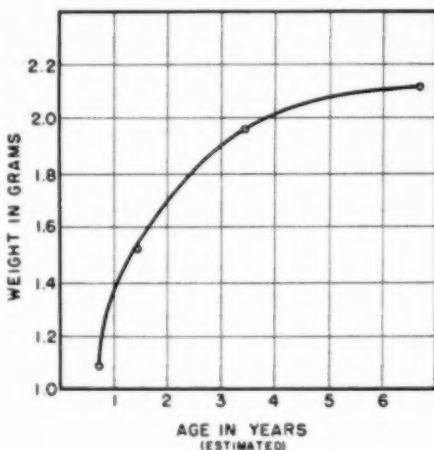
Fig. 4 (Ely). Growth rate of bovine lens.
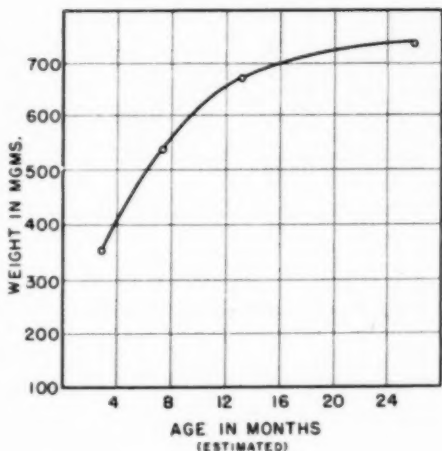
Fig. 6 (Ely). Growth rate of cat lens.

dried lens must be kept in a desiccator during the interval between drying and weighing, if this interval exceeds a few minutes, as the dried residue is somewhat hygroscopic. An increase of 5 to 10 percent in

RESULTS

A compilation of the results obtained is found in Tables 2, 3, and 4. It should be noted that the mean water content of the normal bovine, normal rabbit, and normal

cat lens is between 60 and 70 percent if the two extremes of age are excluded. As the age of the animal increases, the percentage of water decreases. This relationship is shown in Figures 1, 2, and 3. The percentage of water in the lenses of similar age groups in all of the mammals studied is approximately equal, within limits of experimental error.

Figures 4, 5, and 6 show the growth curves of the lenses. A similar type of curve is obtained for each of the three species. The growth rates of bovine lens, rabbit lens, and cat lens agree approximately with the data obtained by Donaldson and King[6] on the Norway rat, if similar age groups are compared. There appears to be little difference in the growth rates of bovine, rabbit, and cat lenses.

DISCUSSION

Lenticular growth occurs by the proliferation of new fibers from the lens bow, with the result that the older fibers are pushed toward the nucleus. As the nucleus is approached these fibers become more inspissated than those peripherally located. Lebensohn[7] found that the cortex of normal ox lens contained 69.9-percent water, while the

nucleus contained only 51.0 percent.

The data presented above show a striking similarity in the water content of the lenses of the three species represented. These percentages are approximately 5 to 8 percent above those found by Donaldson and King[6] for comparable groups of Norway rats. However, the percentage of water of the lens continues to decrease with age in all of the animals studied. Thus the lens is similar to other body tissues in showing an inverse ratio between age and percentage of water.

CONCLUSIONS

1. The mean water content of bovine, rabbit, and cat lenses is between 60 and 70 percent, if the two age extremes are excluded.

2. Growth curves of bovine, rabbit, and cat lenses are similar.

3. The percentage water content of the crystalline lenses of cattle, rabbits, and cats varies inversely with the age and weight of the lens.

4. The percentage water content of the crystalline lenses of comparable age groups of the animals studied is approximately equal, within limits of experimental error.

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METABOLISM OF THE CRYSTALLINE LENS*

II. Respiration of the intact lens and its separated parts

Lawrence O. Ely, M.D.
Iowa City, Iowa

Few studies on the respiration of the intact crystalline lens have been made because: (1) The oxygen uptake of the lens is so small that a reliable result is difficult to obtain, necessitating the measuring of the oxygen uptake for 3 to 6 hours; (2) any prolonged shaking of the lens in the common Barcroft-Warburg flask having a center well causes the lens to disintegrate.

In the few studies that are available the results have not been calculated on a dry-

the substrates were not all alike; little attention was given to the age of the animal; and no record was made as to whether the capsule was intact at the conclusion of the experiment. Later in this paper it will be shown that a significant difference in QO_2[†] is found if the capsule is ruptured.

To aid in the understanding of the metabolism of the lens it is important to know the respiration of the separated parts of the lens. Experimentally the lens may be divided

TABLE 1

Calculated QO_2* of rabbit lens from data taken from the literature

Author	Temp. °C.	QO_2 (wet)	QO_2 (dry)
Mashimo[1]	30	0.260	0.867
Schmerl[2]	37.5	0.0174	0.058
Schmerl[3]	37.5	0.039 –0.113	0.13 –0.377
Kronfeld & Bothman[4]	37.0	0.0174–0.13	0.058–0.433
Field,† et al.[5]	30	0.0203–0.0528	0.066–0.172
	37.0	0.047	0.154
Pignalosa[6]	37.5	0.152 –0.196	0.507–0.65

* The microliters of O_2 consumed per mg. of tissue per hour, assuming an average lenticular weight of 230 mg. and a dry weight of 30 percent.
† Wet weight of 216 mg. and a dry weight of 30.7 percent.

weight basis, but have been given as the oxygen uptake of an entire lens, or as the oxygen uptake per gram of wet weight. From data taken from the literature in Table 1 is shown the calculated QO_2 of the rabbit lens, both on a wet-weight and a dry-weight basis, assuming the average lenticular weight to be 230 mg. and the dry weight to be 30 percent of the wet weight.

Of special interest is the wide range of results, for the dry weight QO_2 ranges from 0.058 to 0.867, a difference of 14 fold. An analysis of these results shows that this wide spread may be due to several factors. The temperatures were not standardized;

conveniently into the capsule, the cortical fibers and epithelium, and the nucleus.

Schmerl[2] first made the observation that the nucleus of a rabbit's lens showed no oxygen consumption over a 2-hour period. The same negative result was found by Pignalosa,[6] Field and others,[5] and Campos.[7] No information was found concerning the respiration of the capsule of the lens of any other animal.

Methods

Rabbit lenses (age 3 to 8 weeks) were used in the measurement of the QO_2 of the intact lenses, while both bovine and rabbit

† Unless otherwise specified QO_2 is defined as the microliters of oxygen consumed per mg. of dry-weight tissue per hour.

lenses were used for the study of the separated parts. The lenses were removed carefully, extreme care being taken to obtain a lens with an intact capsule.

A special Warburg flask was used in this work, by means of which it was possible to shake the lens for 6 to 8 hours without rupturing the capsule. The flasks used were approximately 10 ml. in capacity and had a vessel constant of 0.8 to 0.9. They differed

TABLE 2

THE QO_2 OF WHOLE RABBIT LENS

Lens Number	Calculated Dry Weight	QO_2
1	82.3 mg.	0.06
2	88.6	0.11
3	86.9	0.10
4	81.4	0.17
5	69.9	0.08
6	86.4	0.07
7	98.7	0.09
8	95.5	0.06
9	82.1	0.21
10	101.0	0.08
11	78.5	0.05
12	83.2	0.09
13	105.0	0.10
14	129.0	0.10
15	130.0	0.07
16	98.0	0.07
17	98.5	0.08
18	118.9	0.06
19	122.9	0.09
20	86.1	0.08
21	84.7	0.07
22	76.6	0.12
23	72.9	0.06
24	79.0	0.08
25	82.3	0.09

Mean	0.09
Range	0.05–0.21
S.D.	0.035

from standard flasks in that they had no center wells. The 10-percent potassium hydroxide used to absorb the CO_2 was placed in the side arm along with the usual filter paper. The substrate was a modified phosphate Ringer's solution, pH 7.35, with 200 mg. percent glucose. The temperature of the water bath was 37.5°C. Air was used in the gas space. Measurements were made with both intact lenses and those in which the lenticular capsule had been ruptured with a pithing needle.

Three rabbits of the same age and size were used in each day's determinations. The wet weight of each lens was taken immediately after removal, and only one of the lenses was used for a dry-weight determination. It was assumed that this lens was representative of the percentage of water in all of the lenses of the three rabbits (see "Metabolism of the crystalline lens: I. Water content and growth rate," pages 215-219).

In the study of the separated parts of the lens the capsules were removed by grasping them with a toothed forceps and forcibly
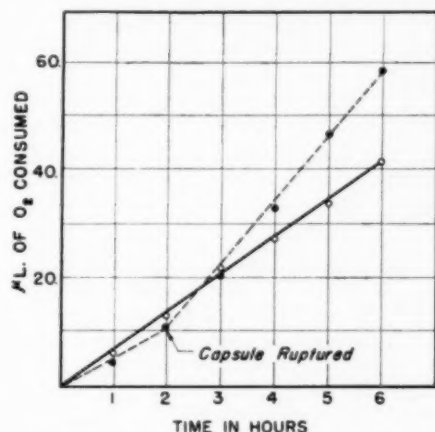
Fig. 1 (Ely). Respiration of whole rabbit lens and effect of rupturing the capsule.

stripping them from the lens. The inner surface of the capsule was scraped with a scalpel so that no epithelium or cortex would remain adherent. One or two capsules were placed in each Warburg flask.

The lenticular fibers were removed by teasing with a dissecting needle. These teased fibers with the epithelium adherent were weighed on a cover slip, and the fibers from each lens were placed in a separate Warburg flask. The fibers of one of the lenses were dried at 104°C. for 48 hours in order to determine the percentage of water. This percentage was assumed to be representative of the water content of the other lens fibers inasmuch as they came from normal animals

of approximately the same age. This assumption was checked by drying the entire contents of a flask at the conclusion of an experiment and subtracting the dried weight of the quantity of glucose buffer used from the dried weight of the entire flask's contents. Less than 2 percent difference was found in the two methods.

After the cortical fibers had been stripped from the lenses, each nucleus was placed in a separate Warburg flask.

Several precautions in the procedures

deviation of 0.034. The range of the QO_2 was 0.05 to 0.21, and accounts for the high standard deviation. Figure 1 depicts a typical effect on the QO_2 due to rupturing the capsule of the lens. This procedure was performed on a total of 15 lenses, and the increase in oxygen uptake which resulted from rupturing the capsule was always between two and four fold.

Table 3 shows a compilation and statistical analysis of the respiration of the separated parts of the lens. It is obvious that neither

TABLE 3

QO₂* OF VARIOUS SEGMENTS OF THE CRYSTALLINE LENS OF BEEF AND RABBITS

| Kind of Lens | Temp. °C. | Nucleus | | Capsule | | Teased Cortex | | | |
| | | | | | | No. of Lenses | QO₂ | | Standard† Deviation |
		Number	QO₂	Number	QO₂		Range	Mean	
Rabbit	37.5	11	0	11	0	20	0.09 0.21	0.145	0.028
Beef	37.5	8	0	8	0	20	0.08 0.26	0.168	0.042

* QO_2 is defined as the microliters of O_2 consumed per mg. of dry tissue per hour.

† Standard deviation, $\sigma = \sqrt{\dfrac{\Sigma x^2}{N}}$

x = deviation of individual items from the mean.
N = total number of cases.

should be noted if reliable results are to be obtained:

1. For valid results in the measurement of the oxygen uptake of the intact lens, no rupture of the capsule should be noticeable at the end of the experiment.

2. In the study of the respiration of the capsules, an oxygen uptake will result occasionally because bits of cortical fibers and epithelium remain adherent if the capsules are not scraped.

3. Care must be taken to remove all cortex from the nucleus or a small amount of respiration will occur.

RESULTS

Table 2 is a compilation of the results obtained in the study of the respiration of the intact lens. The QO_2 of a young rabbit's lens was found to be 0.09, with a standard

the capsule nor the nucleus of the bovine and rabbit lenses respire, or that the oxygen uptake is so low that it cannot be measured by these methods. Teased cortical fibers have a mean QO_2 of 0.145 with a standard deviation of 0.028 for the rabbit lens and 0.169 with a standard deviation of 0.042 for the bovine lens.

DISCUSSION

Because the oxygen uptake of the intact lens increases when the capsule is ruptured, it is possible that the permeability of the capsule is an extremely important factor in regulating the rate of oxygen uptake. Several explanations are possible: (1) The rate of diffusion of oxygen through the capsule may be too slow for the maximal respiration. (2) The substrate may not diffuse through the capsule with sufficient rapidity. (3) The waste products such as CO_2 and lactic acid

may not diffuse out as rapidly as formed and thus retard the oxygen consumption. Further studies on the physical structure and physiologic function of the capsule should be made to clarify this phenomenon.

These studies indicate that the cortical fibers and adherent epithelium are the only part of the lens that respires. The respiration that results may be due to either the cortical fibers or the epithelium, or both. No method has been devised as yet to separate them in order to determine the role each plays in the total respiration. One is led to speculate that the epithelium plays the dominant role in the oxygen uptake, because if any epithelium remains adherent to the capsules that structure exhibits a measurable amount of oxygen consumption.

Conclusions

1. The mean QO_2 of an intact, young rabbit's lens is 0.09, with a standard deviation of 0.035.

2. Rupturing the capsule of the rabbit's lens increases the oxygen uptake 2 to 4 fold.

3. The capsules and nuclei of both bovine and rabbit lenses have a negligible respiration.

4. The QO_2 of teased cortical fibers of rabbit lenses is 0.145, with a standard deviation of 0.028.

5. The QO_2 of teased cortical fibers of bovine lenses is 0.168, with a standard deviation of 0.042.

University Hospitals.

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Discussion

Dr. V. Everett Kinsey (Boston, Massachusetts): Mr. Chairman, Warburg has calculated that diffusion of oxygen becomes limiting in slices of tissue greater than 0.2 mm. in thickness. This shows that the diffusion of oxygen into the lens and carbon dioxide out of this structure are probably limiting factors in the oxygen uptake of the lens. One way of testing this would be for the speaker to plot as a scattergram the weights of the lenses against the oxygen uptake. I made such a plot mentally, as accurately as possible, in the time during which the slide was shown, and was rather surprised to find that the small lenses did not appear to have a greater oxygen uptake per gm. of tissue than did the larger ones. This lack of correlation between higher oxygen uptake and small lenses might be suggestive

evidence of the speaker's hypothesis that most of the oxygen uptake of the lens comes from the epithelium.

Dr. Ely: Field and his co-workers made such a scattergram. They were able to show that there is a decrease in oxygen consumption per gm. of wet weight with an increase in weight of the lens.

I have sufficient data now to show graphically the same thing, and am in preparation of laying out such a comparison. It is going to show with statistical significance, I am sure, if there is a decrease in oxygen consumption with an increase in age.

Such a result would be expected as the nucleus comprises an increasingly greater percent of lens weight as age increases, and the nucleus does not respire.

Dr. David G. Cogan (Boston, Massachu-

setts) : I judge it would be desirable to determine the respiration of the lens epithelium alone but it has been impractical to isolate it. Nevertheless, its volume and number of cells can be readily determined. It would be interesting, then, to calculate the QO_2 on the basis of the volume of the epithelium alone and, assuming that the entire respiration is carried on by the epithelium, to compare this with respiration of epithelial tissue elsewhere in the body.

DR. ELY: Such a procedure has occurred to me several times. In a similar approach, at the University of Wisconsin, Potter has been working on such a problem with Snyder. They actually studied the different parts of cells which had been separated by ultracentrifugation.

By such methods they were able to show that certain enzyme systems were connected with specific structures of the cell. It is quite possible that such a method of separation could be applied to the lens in order to separate the epithelial portion, that is, the nuclear portion, of the cells from the other tissue.

It is also quite possible, as suggested, to calculate the fraction that is represented by epithelium and on such a basis to calculate the QO_2 for the epithelial portion of the lens.

DR. ERNST SCHMERL (Toledo, Ohio) : When I studied the respiration of the lens many years ago, I determined the weight of the lens capsule and considered the possibility that the whole oxygen consumption of the lens might be ascribable to the respiration of the epithelium of the capsule. In this case the respiration of the lens epithelium would be of the same magnitude as that of other epithelial tissues. Rupture of the capsule was found to increase the respiration of the lens.

DR. ELY: Yes, I read your papers and noted the same thing you have mentioned. The way that I circumvented having the epithelium on the capsule, as I pointed out, was by scraping the capsule. I did this because most of the nuclei clung to the cortical fibers. Thus, it became convenient, at least experimentally, to include the epithelium with the cortical fibers, inasmuch as there was no way of getting the epithelium and capsule intact.

FLICKER FUSION FREQUENCY IN AMBLYOPIA EX ANOPSIA*

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Amblyopia ex anopsia is characterized by a defect in visual acuity of one eye, beginning in infancy, often with strabismus. The amblyopia disappears upon occlusion of the dominant eye in children, but not readily in adults. Peripheral acuity and sensation remain normal in field and threshold studies. It is believed that the origin of the amblyopia is in the macular projection of the visual cortex, and that the lesion is of the nature of a suppression or a conditioned reflex.

Although visual acuity is defective, other visual sensations in the central retina appear to be normal.[1] This may limit the lesion more definitely to the cortical layers involved in form vision, preserving the more primitive levels, namely, those for light or brightness contrast, dark-adaptation thresholds, color thresholds, and the capacity of the eye to fixate and localize accurately small points of light on the fovea. Wald and Burian[1] suggested that these layers might be outside the cortex, since in monkeys only pattern vision is lost after cortex ablation.

Visual acuity tests, as performed in the office, test pattern vision. Visual field tests with small targets and good illumination are chiefly tests of pattern vision. When targets are made larger and less contrasting to the background, or if the illumination is reduced, a different sensation, brightness contrast, is being stimulated.

Experiments on the "central" retina in amblyopia may not be exactly central. Wald and Burian found that the amblyopic eye was slightly less capable of centering on a 1-degree target than the dominant eye, and that the threshold curves showed the effect of rod stimulation, although supposedly only

the rod-free area was being stimulated. Eccentric fixation is to be expected in an amblyopic eye. Anomalous correspondence is common. It is possible that a small target may stimulate rods because of ametropia or diffusion or reflection within the eye.[4] This is particularly likely in the dark-adapted eye, where cones are inhibited and rods sensitized.

It has been postulated that fixation is determined not by an anatomic fixed area in amblyopia, but by the visual acuity gradient present. According to Simon (quoted by Weymouth[2]), a normal eye will fixate as much as 2 degrees eccentrically when completely dark adapted. In dark adaptation, the central cones undergo suppression similar to that in amblyopia ex anopsia.

Against this evidence is the fact that introduction of disparity between the central and peripheral retina in experiments with aniseikonia have shown that a distortion of binocular space perception is produced. Retinal correspondence is a fixed and constant phenomenon. Studies of stereopsis and space distortion should be made in dark-adapted eyes.

Ludvigh[3] pointed out that patients with amblyopia ex anopsia first lose acuity, then light differential sensitivity. He proposed that when light differential sensitivity deteriorates, the condition becomes irreversible. However, reversibility is a relative phenomenon, practical under the age of 8 years, possible under the age of 20 years, but improbable over the age of 20 years. Apparently, the primitive visual sensations persist indefinitely.

Flicker fusion frequency is one of the latter. It is the frequency per second below which a flickering light appears to flash intermittently and above which it appears steady. It is a stable and repeatable phe-

nomenon, which can be more easily elicited in unskilled, unapt patients than can visual acuity or field studies.

Figure 1 illustrates flicker fusion. It is an electroretinogram copied from Granit,[5] with flickering stimulation shown below, which gradually decreases in frequency until subjectively (A) flicker begins, and until (B) the recording apparatus can follow. It is evident that if a second flash of light

tients with normal acuity and fields who had brain lesions.

Countless studies have been made of flicker fusion frequency since the time of Plateau.[9] Two accounts of flicker fusion frequency in amblyopia ex anopsia occur in the literature. Lohmann,[10] in 1908, reported that in a young woman, aged 23 years, with amblyopia ex anopsia, the central flicker fusion frequency in the amblyopic eye was
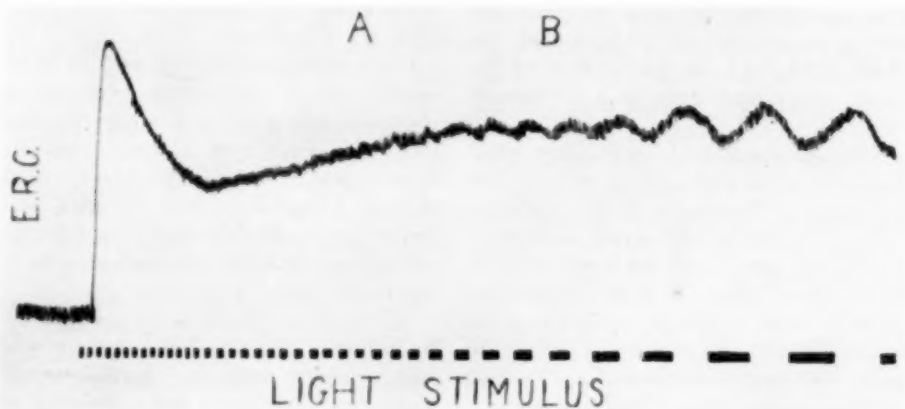
Fig. 1 (Miles). Electroretinogram (Granit) with stimulus of flickering light of decreasing frequency. Subjective flicker at (A) electrical response detected at (B).

occurs before the persisting visual sensation from the first is over, the second is not detected as separate.

It is the phenomenon of the movie screen. If the illumination gets a little too bright, or if the screen is viewed on the peripheral retina, or if the projector shutter is changed to decrease the duration of the flash, or if the flashes decrease in frequency, the movie screen flickers.

Flicker fusion frequency involves not only local rod and cone function, but is influenced by the interaction of various parts of the retina and optic pathway. From the rod-free area, it is low, due to greater visual image persistence. It is much higher from peripheral retina. Phillips,[6] Werner,[7] and Enzer[8] found decrease in flicker fusion frequency in pa-

46 per second, compared to 34 in the normal eye. Visual acuity was: O.D., 5/4; O.S., 5/25. Specifically his results were:

	Central	15°	30°	45° (peripheral retina)
O.D.	34	43	54	57
O.S.	46	43	43	42

Teraskeli[11] reported in 1934 that, in 21 out of 50 cases of amblyopia ex anopsia, the central flicker fusion frequency of the amblyopic eye was equal to that of the periphery 10 degrees out. She concluded that the fovea is lacking in the affected eye, leading to strabismus.

APPARATUS AND METHOD

The present study confirms these flicker fusion frequency findings, and introduces the use of an electronic flickering light

source for clinical studies. There are basic differences in this light source from those used previously. In the past, a rotating disc was used, sectors of which were cut out to permit a flash of light. The disc was motor driven, and the speed was determined by a galvanic speedometer. The moving shutter did not produce an instantaneous shut off and on, as does the electronic device. With the sector disc, the light phase was always directly proportional to the dark phase. With slow speeds, the light interval was longer,
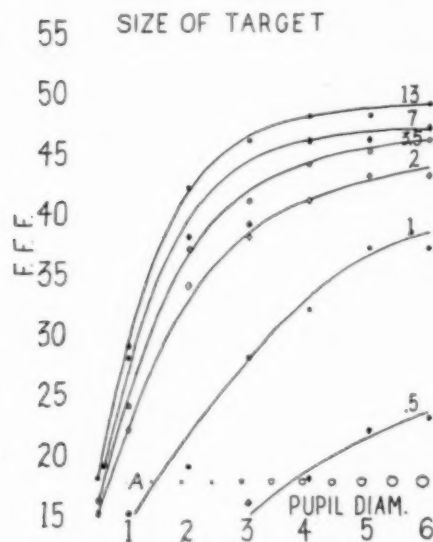
Fig. 2 (Miles). Flicker fusion frequency produced by targets 13, 7, 3.5, 2, 1, and 0.5 cm. in diameter. (A) represents the artificial pupil size.

and the stimulus was, therefore, stronger. The light interval in the electronic instrument used in the present work was 0.010 seconds regardless of the frequency.

This lamp was mounted like a headlight in a reflector. For experimental purposes, the 13-cm. protruding glass crystal was covered by typing paper, 4 cm. from the lamp. The target color was orange-white. The flicker frequency could be read directly from an illuminated dial at the top of the instrument.

This target subtended 8 arc degrees at the distance of one meter used, forming a retinal image of 2.25 mm. Figure 2 shows the results of experiments to determine the ideal size of target for experiments with flicker
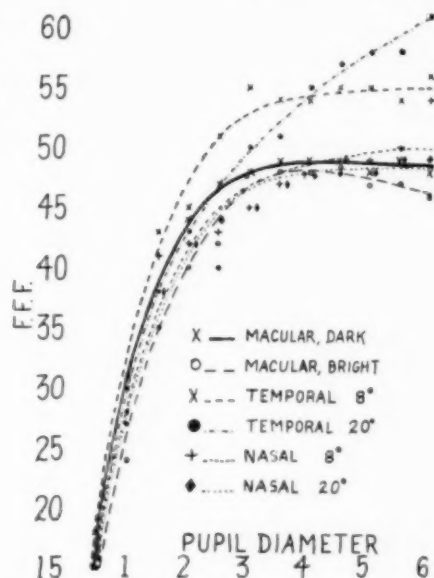
Fig. 3 (Miles). The "macular, dark" line represents the flicker fusion frequency taken with the artificial pupil stick with the room dark and the background dark. The "macular, bright" line is not greatly different, but was taken with the room bright and the background in contrast. The other lines represent the stimulus applied to the peripheral retina.

fusion frequency with this light source. The flicker fusion frequency of subject P. W. M. was taken with central fixation on various sized targets at one meter. Artificial pupils, illustrated at (A), varying in diameter from 0.5 to 6.0 mm., in a strip of brass countersunk to a keen precise edge and painted black, were held 3 mm. in front of the cornea, centered on the target. The marked effect on flicker fusion frequency of decrease in pupil size can easily be seen. Since the retinal image size was constant, this decrease was due to decrease in light intensity.

The flicker fusion frequency was highest, and the curve with pupil size was most precise with the largest diameter target.

The flicker fusion frequency of cones in-
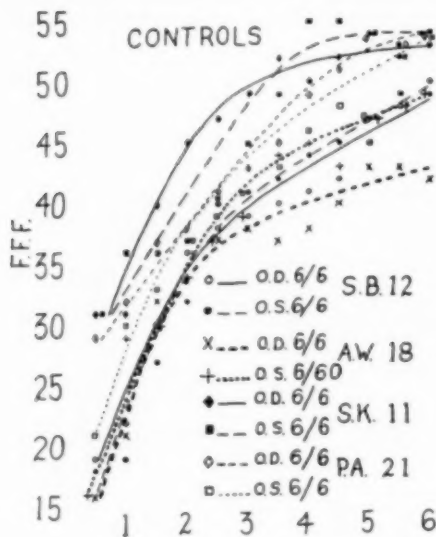
Fig. 4 (Miles). Flicker fusion frequency variation with artificial pupils in three normal individuals and one patient with amblyopia ex anopsia. Note that the flicker fusion frequency curves match in the paired eyes except in A.W., where the normal eye has a low central flicker fusion frequency and the amblyopic eye has a high central flicker fusion frequency.

creases slightly in light adaptation.[13] A more intense small light would be an advantage, but would vary with ametropia, if uncorrected, and would necessitate perfect fixation.

Figure 3 shows the results of experiments made to determine how important contrast and background is in tests of flicker fusion frequency and which areas of the peripheral retina should be selected for routine testing. The subject was P. W. M., and the full 13 cm. target was used. The heavy solid line was taken with the artificial pupil stick as described above, with the room darkened so that the gray walls reflected about 0.5 foot-candles. A black tangent screen was placed behind the instrument.

The curve "o" with wide dashes represents the same experiment except that the room was illuminated to reflect about 25 foot-candles, and contrasting objects were placed behind the instrument. There is slight difference in the curve toward a lower flicker fusion frequency. There was little difference on stimulation of the nasal retina out to 20
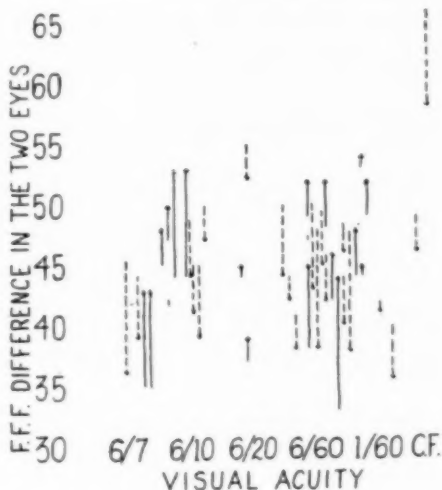
Fig. 5 (Miles). Flicker fusion frequency variation in 43 patients with amblyopia ex anopsia, plotted against the visual acuity. The tail of each arrow represents central flicker fusion frequency of the amblyopic eye, and the head that of the normal. Where that of the amblyopic eye exceeds that of the normal, the arrow is a broken line, and the point is down.

degrees, but a difference of from 6 to 12 flashes per second occurred on the temporal retina. Therefore, the temporal retina was chosen for routine testing.

The tests were carried out on patients as follows: The eye not under test was covered with gauze and black celluloid, and the patient asked to look at the center of the target. The flickering light was speeded up until the patient reported "now," as the light appeared steady. Then the speed of the steady light was decreased until the patient reported flicker. This always proved easier for patients. The average of the difference in the

two readings was recorded as the "precision" of that patient. Usually several determinations were taken. This "precision" was from 1 to 2 flashes per second in most individuals.

The values of flicker fusion frequency for various sized artificial pupils resembles Sloan's[12] curve for light thresholds measured with various sized pupils, especially curve .-.- in Figure 3.

Figure 4 shows the variation of flicker fusion frequency with artificial pupils in three normal individuals and one patient with amblyopia ex anopsia. Note that the flicker fusion frequency curves match in the paired eyes except in A. W., where the normal eye has a low central flicker fusion frequency, and the amblyopic eye has a higher central flicker fusion frequency. The high precision obtained in untrained subjects can be seen on the chart.

Opacities of the media of the eye do not necessarily decrease the flicker fusion frequency. In fact, diffusion may scatter the light to peripheral retina, increasing the flicker fusion frequency. A colorless Maddox rod before an eye reduces acuity to zero, but does not decrease the flicker fusion frequency. On the contrary, one patient, P. G., aged 16 years, had a visual acuity of 6/4 in one eye, a 6-mm. pupil, and glaucoma. Although normal flicker fusion frequency is central 45 and temporal 50, this boy had central 36 and temporal 44.

RESULTS

Forty-four patients with amblyopia ex anopsia were tested. Pupils in each pair of eyes were equal in size. Only 5 patients had pupils under 3 mm. Individual variation proved greater than apparent differences in this series due to pupil size. In each case, the flicker fusion frequency of the amblyopic eye was compared to a perfect control, its normal fellow.

Figure 5 represents the flicker fusion frequency of 43 patients with amblyopia ex anopsia plotted against acuity of the amblyopic eye. The tail of each arrow represents

the central flicker fusion frequency of the amblyopic, and the head that of the normal eye. If the flicker fusion frequency of the amblyopic eye exceeded that of the normal, the arrow is a broken line, and the point is down. If the flicker fusion frequency of the amblyopic eye was less, the arrow is solid and points up. The amblyopic flicker fusion
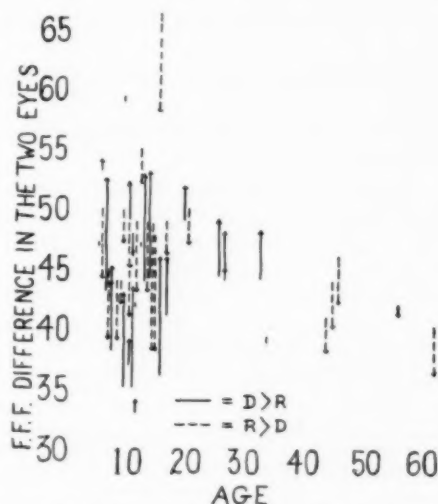
Fig. 6 (Miles). The same data as in Figure 5 plotted against the patient's age.

frequency exceeds the normal slightly, 21 to 18, 5 equal. Most patients had poor acuity, but there is no evident variation in flicker fusion frequency with visual acuity.

Figure 6 shows the same data plotted against the patient's age. There is a tendency for the central flicker fusion frequency to decrease with age, possibly due to smaller pupils. Four of the patients had tropia, one had definite abnormal retinal correspondence, but no significant change from the average is evident.

The average flicker fusion frequency of the normal eye with central fixation was 45.1, of 8-degree temporal retina, 50.4; of the amblyopic eye with central fixation it was 46.4, of 8-degree temporal retina, 50.2. The average increase on shifting stimulation

from central to temporal retina was 5.3 in the normal eye, 3.8 in the amblyopic.

SUMMARY AND CONCLUSIONS

Flicker fusion frequency was determined in 44 patients with amblyopia ex anopsia. The central area of the amblyopic eye performed like the peripheral retina—that is, had a higher flicker fusion frequency than normal. This suggests suppression of central cones.

Normal flicker fusion frequency, with the equipment described in this paper, is 45 flashes per second centrally, and 50 on 8-degree temporal retina.

Defects in central flicker fusion frequency may occur in eyes with 6/4 central acuity, but it may be normal in eyes with 1/60 or

less acuity. Like light and color threshold and contrast, it is considered a primitive sensation, and is received in different centers of the cortex from those involved in visual acuity or pattern vision.

The flicker fusion frequency is easily determined in patients who are unapt in other subjective tests. This test may prove an aid in determining whether certain apparently normal eyes with normal acuity are defective. It may prove useful in studying the function of the retina in patients with opacities of the media. Flicker fusion frequency varies over various parts of the retina, but, unlike field studies, higher sensitivity is elicited in the periphery.

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DISCUSSION

DR. DAVID MAHER (Winnetka, Illinois): Mr. Chairman, there is a great deal of work done in Dr. Miles' review of the flicker fusion frequency. There are a great many questions I would like to ask because I have had some experience with flicker fusion frequency. First as to the type of light or bulb that was used. We have found that by using

a neon bulb, a bulb with neon gas in it, we had a complete on-and-off effect so that we did away entirely with the question of two discs rotating toward each other while there was a gradual loss of illumination as the discs passed each other.

Secondly, he makes the statement that some of the more fundamental conditions of

which the eye has attributes, such as light sense and color sense, are perhaps regarded as better methods of testing lesions in the eye than the visual acuity.

We have been taught and we have found that in amblyopia ex anopsia where there is a loss in visual acuity, there is also a loss of light stimuli and certainly a very definite loss in color stimuli. I would like a little more information on those things.

DR. MILES (closing): The type of bulb that is used in this machine made by General Radio is a gas discharge tube. The light and dark phases are instantaneous cut-offs. I have not had experience with the circular disc method and that is why I stated that these data were definitely not to be correlated with data taken previously.

The light sense and color threshold data were taken by Burian and Wald, published in the AMERICAN JOURNAL OF OPHTHALMOLOGY as noted in my bibliography. They and Lohmann represent the authorities that I have quoted. I have not done work on that subject myself. The biggest question is, in these experiments, whether the amblyopic eye was capable of holding exactly central fixation. A man named Simon in Germany claims that the dark-adapted eye is capable of fixing only on the retinal element which has the highest visual acuity under dark-adapted conditions.

In dark adaptation, the cones and the fovea are inhibited and the rods and the periphery are sensitized so that if fixation depends on the visual acuity gradient, eccentric fixation is to be expected in the amblyopic eye. In any dark-adapted eye, fixation will be eccentric and not centrifoveal. That may have been a source of error in the past on this particular type of patient because we all know that these patients are inclined to anomalous correspondence and are inclined to use extrafoveal fixation. As Burian and Wald pointed out, their experiments on light and color discrimination in amblyopia ex anopsia showed the effect of some rod vision and not just an absence of cone vision, so it is perfectly possible that eccentric fixation could explain the findings in those experiments.

I haven't tried to repeat those experiments myself, so actually all I can report is what I have given you here.

THE ANATOMIC BASIS FOR CERTAIN REFLEX AND AUTOMATIC EYE MOVEMENTS*

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Ann Arbor, Michigan

With progressive phylogenetic development, the dominant level of control of eye movement ascends from lower to higher brain centers and finally to the cerebral cortex. One of the more primitive mechanisms governing ocular movement is that of the vestibular system. The interaction between the vestibular nuclei and the nuclear masses serving the extraocular muscles by way of the median longitudinal fasciculi is present in all vertebrates which have eyes and ears, and extends back in the scale to certain of the Cyclostomes.

As cerebral cortex develops, it assumes a controlling position over the more primitive vestibulo-ocular reflexes. Cortical inhibition has been shown to occur in the rabbit utilizing rotational and postrotational nystagmus as an indicator (Henderson, 1947). In this series of experiments definite inhibition of postrotational nystagmus was produced by allowing ocular function during rotation, probably acting by means of cortical participation in the ocular movement. Such inhibition can conceivably be either voluntary or automatic depending upon the needs of the organism at the moment.

Midbrain dominance over extraocular movement reaches its highest expression in birds, where "consciousness" is said to lie at the mesencephalic level. Here all the sensory stimuli from the body, as well as visual, vestibular, and auditory impulses, are channelled into the tectum of the midbrain, and resultant responses are carried out by way of the tectospinal and tectotegmentospinal pathways. Since the "brain" of the bird above the level of the midbrain consists chiefly of highly developed basal ganglia, control from these higher centers is rela-

tively nonspecific. In mammals, this pattern is reflected by the presence of direct fibers from the retinas which reach the tectum by way of the optic nerves without the interposition of a cortical arc. This makes possible subcortical ocular reflex movements.

The midbrain pattern for ocular movement has been established anatomically in mammals by various workers. This is related to the arrangement of the incoming direct optic-nerve fibers on the one hand, and the nuclear arrangement of the oculomotor and trochlear nerves on the other.

The nuclear arrangement is such that the impulse for elevating the eyes and raising the upper lids arises in the rostral portions of the oculomotor nuclei. The stimulus for turning the eyes downward takes origin in the more caudal portions (the neighboring trochlear nuclei also taking part).

More recent studies (Bender and Weinstein, 1943, Szentagothai, 1942) show a partial reversal of the previously accepted anatomic pattern. These latter investigations have been based upon direct electrical stimulation using a Horsley-Clark type of apparatus where presumably the results could be produced by effects gained through the median longitudinal fasciculi, in which the nuclear masses are embedded. The position of the eyes after destruction of the individual nuclei was not mentioned by these workers.

Experimental studies of the projection of the retinal quadrants on the optic tectum in the rabbit (Brouwer and Zeeman, 1926, Brouwer, 1927), and to a lesser extent in the monkey, have indicated that the inferior quadrants, which are stimulated from the superior visual field, are projected by the optic tracts on the medial and rostral portions of the superior colliculi, and that the superior quadrants, which are stimulated from the inferior visual field, are projected

on the lateral and caudal portions of the optic tectum.

A comparable pattern of projection on this midbrain region was obtained in the rat by Lashley (1934). This pattern would confirm the nuclear localization of the earlier anatomic workers. It acts by direct oculomesencephalic reflex connections in lower mammals without the interposition of a cortical arc. Such direct fiber connections are fewer in number in primates, but it is probable that the pattern is much the same in the monkey. These connections seem to be inoperative or very greatly reduced in man. Nevertheless, their presence and arrangement in lower mammalian forms would serve to confirm the midbrain nuclear arrangement of the earlier workers.

In primates, where the direct oculomidbrain reflex connections are much less important, a cortical arc assumes the major responsibility for reflex ocular movement. This is in disagreement with the older view that many reflex ocular movements in primates have a subcortical origin. Thus automatic eye movements at a cortical level appear to supersede and control the function of both the vestibular and midbrain arcs. Such movements are based upon visual stimuli which reach Area 17 (the striate cortex) by way of the visual pathways.

Experimental work on the monkey (Crosby and Henderson, 1948) shows that a distinct pattern of cortical localization exists in both Area 17 and in Area 19 (the parastriate cortex) which can be related anatomically and functionally to the more primitive midbrain arrangement. The experiments were performed using a very light ether anesthesia and stimulating the brain areas concerned with a faradic current. The directions of ocular movement were recorded in each instance.

Stimulation of the portion of the striate cortex above the calcarine fissure (F, fig. 1) produced a combined conjugate movement down and to the opposite side; of that below the fissure (E, fig. 1), a conjugate

movement up and to the opposite side. This result was that expected from the known cortical pattern of termination of the visual pathway, and confirmed the work of Walker and Weaver (1940).

Area 19 (the parastriate cortex) was shown to have a definite pattern of ocular movement in response to stimulation. Upper Area 19 (A, fig. 1) produced upward conjugate movement, upper-intermediate Area 19 (A', fig. 1) gave movements obliquely upward and toward the opposite side, and middle Area 19 (B, fig. 1) elicited conjugate deviation horizontally toward the opposite side. Stimulation of lower-intermediate Area 19 (C', fig. 1) produced a conjugate deviation obliquely downward and toward the opposite side, and lower Area 19 (C, fig. 1) gave conjugate downward movement.

It must be emphasized that such results required a level of ether anesthesia just below the point where voluntary ocular movement would occur and where the blink reflex to stimulation of the cilia was still present. Deeper anesthesia abolished the upward movements first, then the downward, leaving finally only the horizontal conjugate deviation. Sodium pentobarbital anesthesia was found to carry the monkeys to too deep a level to elicit satisfactory responses. This difference in level of anesthesia may explain the classical view that Area 19 produces only conjugate deviation of the eyes to the opposite side such as was described by Foerster (1931 and elsewhere) in man.

The fiber pathways which link Areas 17 and 19 to the tectum of the midbrain have been termed the internal corticotectal tracts (Crosby and Henderson, 1948). Those from the striate area are designated the occipital division of the internal corticotectal tract, and are further subdivided into dorsal and ventral divisions on the basis of their origin from either above or below the calcarine fissure.

These tracts sweep forward in a layer just outside the visual radiations and parallel them as far forward as the pulvinar of the
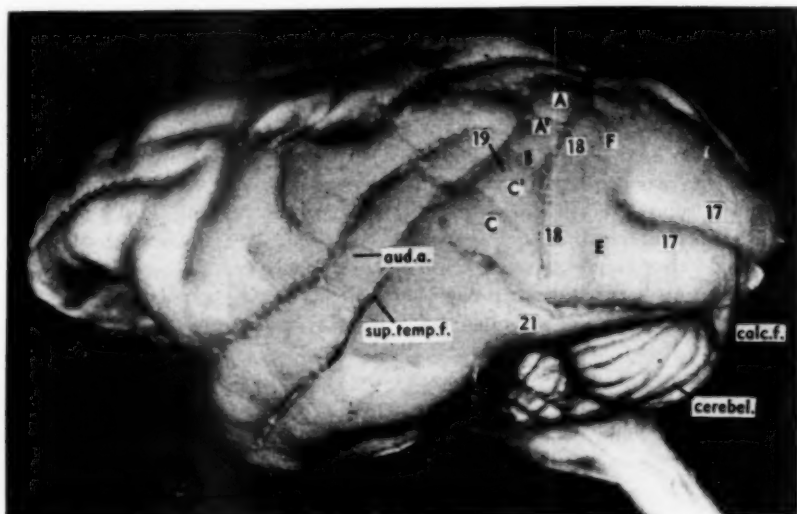
Fig. 1 (Henderson). The left side of the brain of a Macaca mulatta as shown in a photograph (×1.8). Areas 17, 18, 19, and 21 are designated. On Areas 17 and 19 the various points from which eye movements were elicited are indicated by letters (see text). (Reproduced by permission of E. C. Crosby and J. W. Henderson: J. Comp. Neurol., **88**:53-92, 1948.)

ABBREVIATIONS FOR FIGURES

aud. a., auditory area.
calc. f., calcarine fissure.
caud. n., caudate nucleus.
cer. ped., cerebral peduncle.
cerebel., cerebellum.
corp. cal., corpus callosum.
cort. teg. tr., corticotegmental tract.
cort. tect. tr., aud. div., corticotectal tract, auditory division.
ext. cort. tect. tr., external corticotectal tract.
F, fornix.
fim., fimbria.
hip., hippocampus.
hip. g., hippocampal gyrus.
int. cort. tect. tr., oc. div. dors. p., internal corticotectal tract, occipital division, dorsal part.
int. cort. tect. tr., oc. div. vent. p., internal corticotectal tract, occipital division, ventral part.
int. cort. tect. tr., preoc. div. dors. p., internal corticotectal tract, preoccipital division, dorsal part.
int. cort. tect. tr., preoc. div., vent. p., internal

corticotectal tract, preoccipital division, ventral part.
m. l. f., medial longitudinal fasciculus.
med. lem., medial lemniscus.
med. tect. sp. tr., medial tectospinal tract.
n. III, oculomotor nucleus.
op. tr., optic tract.
ped. inf. col., peduncle of inferior colliculus.
pul., pulvinar.
str. med. prof., deep medullary stratum.
str. term., stria terminalis.
sub. nig., substantia nigra.
sup. cerebel. dec., decussation of superior cerebellar peduncle.
sup. temp. f., superior temporal fissure.
tect. oc. tr., tecto-oculomotor tract.
tect. pont. tr., tectopontine tract.
tect. teg. tr., tectotegmental tract.
vis. rad., visual radiations.
x, termination of occipital division of internal corticotectal tract in superior colliculus.
y, termination of preoccipital division of internal corticotectal tract in superior colliculus.

thalamus. Here they turn medially across the internal capsule, through the pulvinar, and

terminate in the tectum of the midbrain (fig. 2). Those from the upper calcarine
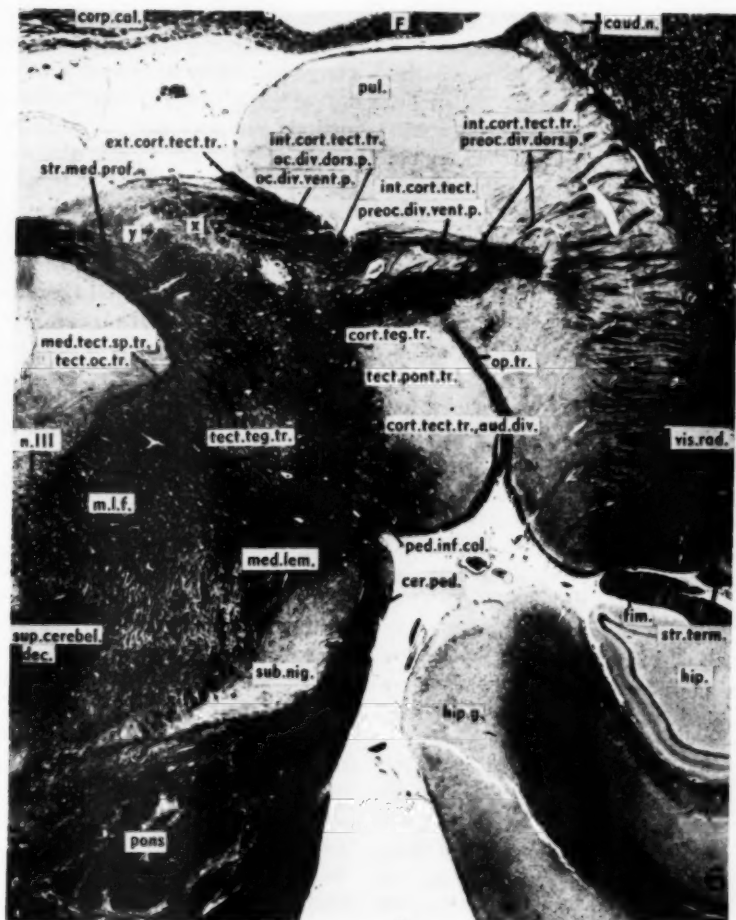
Fig. 2 (Henderson). A photomicrograph of a section near the rostral end of the superior colliculus from a transverse series of a Macaca mulatta brain stained by the Weil technique (×4). For a more comprehensive series see Crosby and Henderson, 1948. (Reproduced by permission of E. C. Crosby and J. W. Henderson: J. Comp. Neurol., 88:53-92, 1948.)
See Fig. 1 for explanation of abbreviations.

area (dorsal division) reach the caudal portions of the tectum, and those from the lower calcarine area terminate in the more rostral tectum of the midbrain. Thus the dorsal division relates inferior visual field, superior calcarine area, and caudal tectum to the more caudal portion of the oculomotor complex. Conversely, the ventral division relates superior visual field, inferior calcarine area,

and rostral tectum to the more rostral portion of the oculomotor nucleus. The expected responses in reflex ocular deviation to stimuli lying in the visual field can therefore be related anatomically.

The internal corticotectal tracts from Area 19 have been designated the preoccipital division, which likewise is divided into dorsal and ventral parts based on origin either from

upper or lower parastriate cortex (fig. 2).
These fibers course forward to pulvinar
levels along with the occipital division in the
same layer just outside the visual radiations.
The dorsal portion can be traced to the ros-
tral tectum, while the ventral part reaches the
more caudal tectum. Thus an interrelation-
ship between upper Area 19 and rostral ocu-
lomotor nucleus can be seen, and, conversely,
between lower Area 19 and caudal oculo-
motor nucleus.

The pathways described were traced both
in normal anatomic preparations and by ex-
perimental degeneration. It has previously
been noted (Kronfeld, 1929) that they fol-
low the visual radiations forward, but the
fact that cortical localization can be related
to the anatomic pattern of arrangement of
the extraocular muscle nuclei has, to the best
of our knowledge, not been heretofore noted.

It is interesting that the termination of
such fiber tracts fails to confirm the more
recent work on the arrangement of the oculo-
motor nuclear complex. The parallel course
of the tecto-oculomotor fibers which carry
the impulses into the various portions of the
oculomotor nucleus speaks against any re-
versal of pattern within the midbrain itself.

The fact that the pattern described for
Area 19 is inverted from that of Area 17
can be explained by the presence of short
association bundles which can be seen to
connect lower Area 17 with upper Area 19,
and vice versa.

Both the occipital and preoccipital divi-
sions of the internal corticotectal system
were seen to give off fibers which turned
into the tegmentum of the midbrain without
reaching the tectal areas (cort. teg. tr., fig.
2). These lay midway between the dorsal
and ventral portions of both divisions in
their course forward from the occipital lobe
and presumably relate the areas for hori-
zontal movement with the abducens complex
by means of tegmental pathways. They could
be traced with certainty only as far as the
inferior collicular level.

Judged by the relatively great number of
corticotectal and corticotegmental pathways,
a large percentage of normal eye movements
can be explained as visual automatisms—
cortical, yet subconscious in a voluntary
sense. This would include the movements
subserving fixation, since it is well known
that injury to Area 19 interferes with the
holding of fixed gaze.

McCulloch (1944) has shown that cortical
conduction occurs from Area 8 of the frontal
cortex to the parastriate area, but not in
the opposite direction. This places the corti-
cal centers for automatic eye movements
under the control of the voluntary motor
centers, with Area 8 able either to utilize
the direct corticobulbar pathway to the brain
stem, or to exert a modifying effect upon
the cortical ocular automatisms by way of
the parastriate area. It should be stressed
that higher centers utilize previously laid-
down mechanisms for the control of ocular
movement. In each instance, the more primi-
tive pattern can be recognized, but is made
use of by more recent phylogenetic brain
centers.

It should be noted that there is a differ-
ence in level between the internal cortico-
tectal fibers entering the tectum of the mid-
brain and the corticobulbar fibers which lie
just above the cerebral peduncles. Since the
fibers from the occipital lobe are more super-
ficial in the colliculus, pressure downward
from above should affect the reflex ocular
movements much earlier than those which
have a voluntary origin from Area 8 of the
frontal lobe. Thus there should be a differ-
ence noted between command movements of
the eyes and following movements in such
an instance.

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DISCUSSION

DR. DAVID G. COGAN (Boston, Massachusetts): I would like to ask two specific questions and I hope they weren't covered in the paper. I was so interested in some of the parts I may have lapsed in the others.

Did you mention what the threshold was in Areas 17 and 19? It seems to me there has been some conflict between what Walker and Weaver and what others have found in the relative thresholds in 17 versus 18 and 19.

Also, it seems to be anomalous that there should be such a reversal of vertical representation in 19 and 17. You say that that is executed by means of intracortical association pathways but it seems to me curious in the economy of the nervous system that such a reversal should take place.

DR. P. J. LEINFELDER (Iowa City, Iowa): I want to congratulate Dr. Henderson on a very difficult piece of work. I am sure he has labored much more extensively than you might realize from seeing the few slides that he has shown.

The importance of his contribution, I think, should not be estimated in terms of its applicability to any one lesion of the

nervous system, but rather in his confirmation of the intimate reflex association between vision, binocular vision, and the ocular motor system.

He has demonstrated the pathways that carry the impulses for adequate coördination of ocular movements and fixation.

DR. PIERRE DANIS (Brussels, Belgium): I think the localization of the muscles he referred to is still open to question because I think you base your general opinion on the work of Brouwer but you have other workers who gave a reverse pattern. Bach and von Biervliet gave a reverse pattern, too.

DR. HENDERSON (closing): I would like to answer Dr. Cogan's questions first while I have them in my mind more specifically. The difference in threshold actually does exist. It is not something to be measured in any specific terms. If we had the current and stimulation high enough, we would get movement which we attributed to Area 17 by a spread from Area 19, which was of that type. Also the work of Walker and Weaver was performed under a light anesthesia, as I recall, which again brings the question of anesthesia into it.

The problem of the difference between Areas 17 and 19 bothered me, too. The pathways I think are there all right. There is no question about the association pathways being there but why two different areas so closely related should have inverse correlation with the midbrain arrangement I do not know.

However, the fact that the stimulus which comes back and influences automatic movements comes from Areas 8 to 18 and then into 19 would indicate that perhaps 19 is more related to the voluntary centers while 17 is related to the visual receptive pattern. We know that there are the two different sets of pathways that run forward into the midbrain; this may have some bearing on the reversal of pattern.

As Dr. Danis has said, there has been an argument about the nuclear localization all along. This includes the work of Brouwer, of Bernheimer, of Starr, and several others, all of whom to a greater or lesser extent destroyed individual muscles and looked for individual nuclear degeneration. That, to the anatomist, is incontrovertible. To the physiologist, perhaps, it is not. It has also raised the question in my mind, which may be just "woolgathering," as to whether the inverse difference between these physiologic and anatomic patterns is going to make us change our conception of what is going on.

Is the primary thing that is happening the contraction or is the primary thing the inhibition? Perhaps that might have some bearing on the ocular movements. I know there isn't a good way of reconciling the two views but we are hoping that further work will help in bringing the two views closer together.

COMPRESSION TESTS ON AQUEOUS VEINS OF GLAUCOMATOUS EYES*

APPLICATION OF HYDRODYNAMIC PRINCIPLES TO THE PROBLEM OF INTRAOCULAR-FLUID ELIMINATION

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Although nothing similar to the diagnostic clues obtained in glaucoma by the use of the ophthalmoscope, perimeter, and tonometer can be pointed to in the field of gonioscopy and biomicroscopy, sufficient evidence has accumulated to permit the hope that eventually the aqueous veins and their roots deep inside the scleral tissue will become significant for the understanding, if not also for the early diagnosis, of glaucoma.

Since intraocular fluid can be seen streaming in the biomicroscopically visible aqueous veins,[1] we are allowed to approach the glaucoma problem from a new viewpoint.[3-5] The work of recent years[2, 6-12] has added confirmation to our assumption that the intraocular-fluid elimination can be studied biomicroscopically, and increasing attention is being given to the aqueous veins.[13-20]

While different new roads may lead to a more lucid interpretation of the inexhaustible glaucoma problem, up to this time pertinent information has been made available in three directions: Gartner[6] initiated photographic recording of the influence on aqueous veins of miotics, a method which, in the future, may reveal conclusive evidence of pharmacologic effects on glaucomatous eyes.

Secondly, the fundamental compression test of the recipient vessel of aqueous veins (reference 1, p. 36; references 3, 4, and 5; reference 11, p. 78f.) revealed differences in the results obtained on glaucomatous eyes as compared to those obtained on eyes with normal intraocular pressure.

Thirdly, the increment-pressure test, performed on the cornea and observed on aqueous veins or better on recipient vessels, promised further differentiation in the response of glaucomatous eyes and eyes of normal pressure.

In this paper, the effect of miotics and of other drugs on the aqueous veins will not be discussed; this does not mean that previous investigations[3, 21] have answered sufficiently all pertinent questions. We shall restrict our discussion to the second and third topics, the compression test on the recipient vessel, and the increment-pressure test on the cornea.

COMPRESSION TEST ON THE RECIPIENT VESSEL

After compression of the recipient vessel of an aqueous vein either one of the following phenomena will be observed: clear fluid may expel the blood from the blocked area or, in other aqueous veins, all clear fluid may become expelled by blood. The first phenomenon was formerly called—for purely descriptive purposes—the glass-rod phenomenon (reference 1, p. 36); this name was chosen because of the similarity of the vessel filled by clear fluid to a glass rod. The opposite effect, entrance of blood into the blocked vessel section, was called the negative glass-rod phenomenon.

These terms, although accepted,[2, 11, 16, 20] and in most instances well understood, are not clear enough to exclude occasional misunderstandings. Therefore, a more unequivocal expression will be substituted. Instead of "positive glass-rod phenomenon" we shall use the expression "aqueous-influx phenomenon," and the term "negative glass-rod

phenomenon" will be replaced by "blood-influx phenomenon."

Both the aqueous-influx and the blood-influx phenomena were shown[3-5, 11] to be due to pressure differences which prevail between the two fluids running in the same vessel parallel to each other and to the vessel wall, namely aqueous humor and blood.

To De Vries's thorough and scholarly monograph we owe the first photographic recording of the blood-influx phenomenon. The response to the compression test is characteristic for each individual aqueous vein; that is, the result is the same when the test is repeated after months and years. Only under pathologic conditions, the result of the compression test, and even the appearance of the undisturbed aqueous vein, may change. Hyperemia may temporarily conceal the clear stream in an aqueous vein; the latter will reappear again when the eye assumes its previous appearance.

It has been found[3-5, 11] that the aqueous-influx phenomenon does not appear in glaucomatous eyes as long as the intraocular pressure remains elevated. This, however, is not a quality restricted to glaucomatous eyes; the blood-influx phenomenon occurs as well in eyes with normal intraocular pressure but, in glaucomatous eyes, it is the regular response of an aqueous vein subjected to the compression test on its recipient vessel.

In only one eye out of the series studied by De Vries[11] an aqueous-influx phenomenon was found in spite of the presence of glaucoma; this eye, however, was observed during a period of decrease of intraocular pressure. This is a confirmation of previous observations which revealed that in eyes suffering from primary compensated glaucoma, aqueous veins fail to show the aqueous-influx phenomenon; after successful surgery, or after response to miotics, the same aqueous vein which showed a blood-influx phenomenon, may show an aqueous-influx phenomenon. In patients suffering from unilateral glaucoma, the fellow eye with normal intraocular pressure may show an aqueous-influx phenomenon while a symmetrically located aqueous vein in the glaucomatous eye will show the blood-influx phenomenon.[3, 4]

With an increase of the intraocular pressure, a longer or wider stream of clear fluid might be expected in the aqueous veins of glaucomatous eyes, provided the chamber angle is open.[22] It has been found, however, that the clear fluid in aqueous veins of glaucomatous eyes and in their recipient vessels does not extend farther nor expand wider than in eyes with normal intraocular pressure. This fact and the absence of the aqueous-influx phenomenon on glaucomatous eyes prove that the aqueous flow in the aqueous veins of glaucomatous eyes is less vigorous than in eyes with normal intraocular pressure. Together, these facts suggest the presence of an obstacle to the intraocular-fluid elimination, located somewhere between the anterior chamber and the biomicroscopically visible aqueous veins.

INCREMENT-PRESSURE TEST ON GLAUCOMATOUS EYES

Both Goldmann[9] and De Vries[11] extended, independently from each other, an observation published by one of us, namely that pressure applied externally to the eyeball but not to an aqueous vein may increase the flow of clear fluid in aqueous veins and in recipient vessels (reference 23, p. 1197).

Applying a dynamometer to the lower lid, De Vries observed regularly an increase of flow in the aqueous veins. Far from the site of an aqueous vein, he pressed a dynamometer onto the temporal extremity of the lower lid while a nasally located aqueous vein was watched biomicroscopically. When a dynamometer pressure of 30 gm. was exerted upon the lower lid, the clear stream in the aqueous vein, far from the compressed area, became faster and, inside the aqueous vein, the clear fluid content increased and the blood content decreased. Discontinuation of the dynamometer pressure was immediately followed by mingling of the aqueous

and sanguineous vessel content so that an undivided stream of diluted blood became visible. After a few seconds, however, the original distribution of blood and aqueous humor reappeared as it was seen prior to the compression.

This approach has been carried further by Goldmann.[9] He exerted graduated pressures against the center of the cornea by means of a spring balance, watching until an aqueous vein under biomicroscopical observation showed visible dilatation of its clear content. The anesthetic used for this examination was not mentioned, but it is known[21] that all drugs instilled into the conjunctival sac alter the appearance of the aqueous veins. Goldmann observed a widening of the clear stream in aqueous veins when a 5- to 12-gm. increment of pressure was exerted upon the cornea. The average of 8 gm. additional pressure corresponds, according to Goldmann's calculation, to an intraocular pressure increase of 10.4 mm. Hg.

Goldmann believes that the actual pressure difference between anterior chamber and anterior ciliary veins in the normal human eye is one half to one fourth of the value obtained with his increment-pressure method. For the pressure difference between chamber and ciliary veins, he uses the expression "outflow pressure"; for the increment-pressure values obtained by observation of aqueous veins, he proposes the term "scheinbarer Abflussdruck" which means "apparent outflow pressure."

Goldmann found increased values of "apparent outflow pressure" in eyes suffering from compensated glaucoma even when the intraocular pressure was normalized by drugs. In eyes suffering from acute glaucoma, however, the "apparent outflow pressure" was normal after successful use of miotics. The pressure values in glaucomatous eyes were above 20 gm., most of them between 26 and 30 gm.

However interesting these results appear, they are much less convincing when the whole series of facts is closely sifted. Then it will become manifest that the high values of "apparent outflow pressure" are not at all restricted to glaucomatous eyes. In the second paragraph of page 84,[9] there is a phrase printed in italics and saying that very narrow aqueous veins showed markedly higher values and, therefore, "they should not be used for these experiments." In a footnote on the same page, Goldmann mentioned that recipient vessels of eyes with normal intraocular pressure, located in the inferior parts of the eyeball and conspicuous by slow current, may show "anomalously high" readings.

From these exemptions it becomes evident that Goldmann arbitrarily decided to consider as normal values exclusively those in the lower ranges of his spring-balance readings despite the fact that markedly higher values were also obtained on eyes with normal intraocular pressure. Therefore, the figures listed in Goldmann's tables are not conclusive for the pressure gradient prevailing between anterior chamber and anterior ciliary veins; they may be characteristic of the individual aqueous vein which was observed in each single experiment.

More confusion is created by the repeated omission of the adjective "apparent" before the noun "outflow pressure" whereby the impression arises that the real outflow pressure has been measured. Therefore, we should prefer to term the values reported by Goldmann "increment pressure" rather than "apparent outflow pressure." This increment pressure will depend upon different factors, the most important of which seems to be the vessel diameter (see under "Hydrodynamics").

It is very probable that all aqueous veins with high increment-pressure readings are either narrow throughout their course—as those mentioned by Goldmann[9] in the second paragraph of page 84—or that they have a localized constriction or narrowing somewhere in their roots. A sclerosis of the trabeculum could also be held responsible

for high increment pressure readings if found in all aqueous veins of the same individual eye; this, however, is in contradiction to facts known about the backflow phenomena into the canal of Schlemm.

GONIOSCOPY AND AQUEOUS VEINS

For more than three decades ophthalmologists have been fascinated by gonioscopy, a method to which many interesting facts are owed. It seems, however, that as far as glaucoma problems are concerned too far-reaching conclusions were drawn from gonioscopic findings. Magitot,[17, 25] Busacca,[26] and also one of the pioneers in gonioscopy,

angle glaucoma, however, cannot even be attempted on the basis of gonioscopy. Here, it seems that observations on aqueous veins may fill a gap in our understanding. While Schlemm's canal is accessible to intravital examination by means of gonioscopy, the outlets of the canal themselves are not visible intravitally; only ascending branches, connecting them with the episcleral meshwork, become accessible to biomicroscopic examination. Thus, biomicroscopy and gonioscopy complement each other to further our knowledge of the admirable exhaust system which consists of the canal of Schlemm and its outlets.

TABLE 1

EFFECT OF WIDTH OF CANAL OUTLETS AND OF AQUEOUS VEINS

	A. With Wide Outlets	B. With Narrow Outlets
1. Gonioscopic findings Backflow of blood into the canal of Schlemm	Frequent	Rare
2. Biomicroscopic findings		
a. Rate of flow of aqueous humor, observed on recipient vessel	High	Low
b. Compression test, performed on recipient vessel, observed on aqueous vein: Influx phenomenon	Aqueous influx	Blood influx

c. Increment-pressure test, performed on cornea,
     observed on recipient vessel: Dynamometer
     readings
	Low	High

3. Intraocular pressure Tonometer readings:	If no other pathologic condition: normal	If many outlets narrow: high

Troncoso,[16] (page 231) have sounded impressive warnings. Busacca has not been able to detect signs characteristic of glaucoma in the chamber angle. He concluded that the part played by the iridocorneal angle in the pathogenesis of glaucoma is insignificant. Troncoso stressed the fact that shallowness of the chamber angle is only a predisposing factor and cannot be the primary cause of acute glaucoma, as recent writers have been inclined to believe. Kronfeld[27] conceded that the gonioscopic findings do not always enable one to tell with certainty whether the anatomy of the chamber angle has been altered to such an extent that the function of the normal channels of outflow is permanently or irreparably impaired.

The explanation of the so-called vide-

It may well be that a different trend of gonioscopic examination will yield more useful results than the observations of the anatomic relationship between corneoscleral tissue, on one side, and uveal tissue, on the other, have furnished during the last decades.

Gonioscopy proved[28, 29] that blood rarely entered the canal of Schlemm of glaucomatous eyes; whereas, in eyes with normal pressure, the canal often showed the presence of blood in varying amounts. If an obstacle were situated between the anterior chamber and the canal of Schlemm (that is, in the trabecular meshwork), blood could still enter the canal. The ease of blood backflow into the canal of normal eyes, and the rarity of the same phenomenon in glau-

comatous eyes,[28, 29] could be explained tentatively by obstruction of visibility of the canal in shallow-angle eyes; such an explanation, however, cannot be valid for Kronfeld's[29] (page 1167) experiments performed on eyes which suffered from wide-angle glaucoma.

An impediment to flow, located somewhere between the canal of Schlemm and the deep scleral venous meshwork, is to be postulated. If this impediment were situated in the trabecular area, a relatively low pressure should be expected inside the canal of Schlemm, and there would be no reason why blood should not easily gush into the canal. Only a narrowing of the outlets or a marked decrease in their number can explain, the missing backflow of blood into the canal together with the high increment-pressure readings, the absence of a longer or wider aqueous stream in the biomicroscopically visible elimination pathways, the absence of the aqueous-influx phenomenon in glaucomatous eyes and, possibly, even the intraocular-pressure increase due to insufficient fluid elimination (Table 1).

APPLICATION OF HYDRODYNAMIC PRINCIPLES TO THE PROBLEM OF INTRAOCULAR-FLUID ELIMINATION

If one considers from the point of view of hydrodynamics the system comprising Schlemm's canal, its outlet tubes, and the conjunctival and anterior ciliary veins into which they finally empty, it is possible to list a number of factors that may influence the rate of discharge of aqueous humor from the canal and hence may also affect the intraocular pressure. Such a list, not necessarily complete, is given in Table 2.

The question now arises as to the relative magnitudes of the effects of these factors. For making the comparisons, we use Poiseuille's equation for the rate of streamline flow of a viscous liquid through a sufficiently long straight tube of circular cross section:

(1) $\dfrac{Q}{t} = \dfrac{\pi r^4 \Delta p}{8 \eta l}$,

where Q is the quantity of liquid of viscosity η, flowing in time t through a tube of radius r and length l under the influence of a pressure difference Δp ($= p_o - p_1$) between the ends of the tube, where p_o is the pressure at the origin and p_1 the pressure at the emptying point of the tube. We use the values

TABLE 2
SOME FACTORS AFFECTING THE RATE OF DISCHARGE OF AQUEOUS HUMOR FROM THE CANAL OF SCHLEMM

A. Number of outlet tubes, part of them becoming visible aqueous veins
B. Rate of flow per tube, dependent on:
   1. Radius of tube, including effect of enlargements, contractions, or obstructions
   2. Distensibility of tube
   3. Shape of cross section of tube
   4. Length of tube
   5. Straightness of tube
   6. Nature of tube inlet and outlet
   7. Branching of tube
   8. Pressure in Schlemm's canal
   9. Pressure in the conjunctival and episcleral veins at point of junction with aqueous veins
   10. Temperature gradients across the veins
   11. Diffusion and osmotic effects
C. Viscosity of aqueous humor, dependent on its
   1. Composition, in turn dependent on
      a. Salt content
      b. Protein content (dissolved in the fluid or present as blood corpuscles)
   2. Temperature, dependent on exposure of the veins to
      a. The temperature of the interior of the eye
      b. The temperature at the surface of the eye
      c. Rate of flow of the liquid
      d. Thermal conductivity of the covering tissues

shown in Table 3 as typical for the normal human eye. A simple calculation shows that these data are reasonably self-consistent.

We consider first the effect of the number (n) of the outlets, assuming the other variables to remain constant. An adaptation of the Poiseuille equation gives:

(2) $\left(\dfrac{Q}{t}\right)_{total} = \sum_{i=1}^{n} \dfrac{\pi r_i^4 \Delta p_i}{8 \eta l_i}$

If n is taken to be the only variable this becomes:

(3) $\left(\dfrac{Q}{t}\right)_{total} = \dfrac{n \pi r^4 \Delta p}{8 \eta l} \approx 18.8 \text{mm.}^3/\text{min.}$

This value is of the same order of magnitude, although somewhat higher than the

TABLE 3

p_o: pressure at origin of outlets of Schlemm's canal ≈ 20 mm. Hg
p_1: pressure at junction of outlet or aqueous vein with recipient vein ≈ 10 mm. Hg
l: length of outlet plus aqueous vein ≈ 2 mm. (range 1–10 mm.)
η: viscosity of aqueous humor—0.00715 poise (the approximate value for one percent sodium-chloride solution at 37°C. or 98.6°F.)
r: radius of circular outlet (most of them are elliptic, see later) assumed ≈ 0.013 mm.
a: major semiaxis of elliptical outlet ≈ 0.0169 mm. (many of them are larger)
b: minor semiaxis of elliptical outlet ≈ 0.010 mm. (many of them are wider, some are smaller)
Q/t: rate of flow of aqueous humor from Schlemm's canal ≈ 18.8 mm.^{3} per min. for 30 tubes or about 0.626 mm.^{3} per min. for one tube
n: number of separate outlets ≈ 30.

values found by previous investigators.[24] We take n to be equal to 30 for the typical normal human eye, and use this equation to calculate Δp, the pressure drop along the tube, as a function of n for a constant outflow rate. The results are given in Table 4 and in Figure 1.
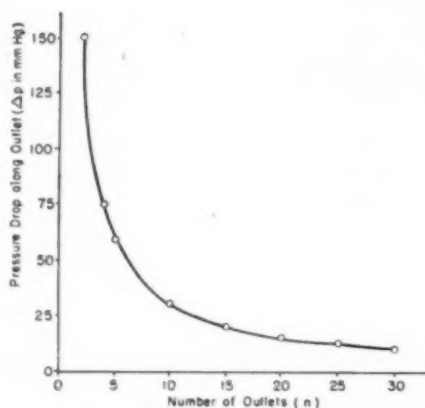
Fig. 1 (Ascher and Spurgeon). Dependence of pressure drop on number of outlets.

It can be seen that, for other factors remaining the same, a decrease of about 50 percent in the number of outlets leads to the upper limit of normal values of Δp, the pressure drop, and hence of p_o, the pressure at the origin of the outlet in Schlemm's canal. Further decrease of the number of outlets may cause a definitely dangerous increase in Δp. In the extreme case of no outlets Δp, p_o, the pressure in Schlemm's canal and, therefore, the intraocular pressure becomes very great or the outflow rate decreases markedly, or both.

The next factor to be considered is the most important one from the hydrodynamic point of view: the radius (r) of the outlet and of the aqueous vein. Its outstanding importance lies in the fact that it occurs to the fourth power in the Poiseuille equation; whereas, the other factors occur to the first power only, or else as relatively small cor-

TABLE 4

DEPENDENCE OF Δp ON NUMBER OF OUTLETS

Number of Outlets, n.	Pressure Drop along Outlet (Δp in mm. Hg)	Pressure at Origin of Outlet (p_o in mm. Hg)
30	10	20
25	12	22
20	15	25
15	20	30
10	30	40
5	60	70
4	75	85
2	150	160

rections of the equation. For constant values of η, l and Q/t, the effect of radius change on pressure is shown in Table 5 and Figure 2.

It is seen that as r decreases from the assumed norm, Δp, the pressure drop, increases enormously, if the other factors remain unchanged. Assuming p_1, the pressure in the recipient vein, to remain unchanged, p_o, the pressure in Schlemm's canal must, therefore, also increase very rapidly as r decreases if the same rate of outflow is to be maintained. The value of p_o could become seriously high for a decrease of r of only three microns, that is, from 13μ to 10μ.

These calculations were based on the assumption that all outlets have the same radius. Actually, of course, this is not true, and it becomes of interest to calculate the relative outflow from tubes of various sizes. As a simple case, consider a set of 30 tubes arranged "in parallel," 27 of them having a radius of 0.006 mm., corresponding to the smallest minor-axis values measured by Theobald,[32] and three of them having radius 0.026 mm., the other variables remaining unchanged. For a value of Δp of 10 mm. Hg, the 27 small tubes could carry 0.768 cubic millimeters per minute of aqueous hu-

TABLE 5

EFFECT OF RADIUS CHANGE ON THE
PRESSURE DROP, Δp

Radius of Outlet (r in μ)	Pressure Drop Along Outlet (Δp in mm. Hg)	Pressure in Schlemm's Canal (p_o in mm. Hg)
15	6	16
13	10	20
10	28	38
9	44	54
8	70	80
7	119	129
6	226	236
5	456	466

mor, whereas, the three large tubes could carry 30.1 cubic millimeters per minute. In other words, the three large tubes could carry about 40 times as much liquid as the 27 small tubes. If the three large tubes were destroyed, Δp would have to increase to 402 mm. Hg to maintain the same total outflow rate through the small tubes. It is not meant to imply that the same total outflow rate must be maintained or that the pressure increase would actually amount to 402 mm. Hg. The point is that destruction of the three large tubes would very greatly increase the resistance to flow of the aqueous humor.

So far the discussion has concerned only tubes of uniform cross section. We now inquire as to the effect if there is a constriction or an obstruction in a relatively large tube. Such a tube can be considered as a large and a small resistance to flow, joined in series (fig. 3). The Poiseuille equation can be applied to each part separately. As an example we may calculate the pressure drop along each section of the tube shown
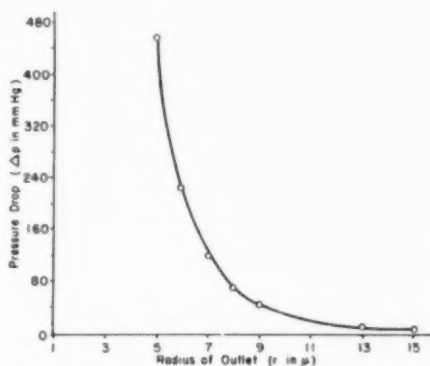
Fig. 2 (Ascher and Spurgeon). Effect of radius change on the pressure drop, Δp.
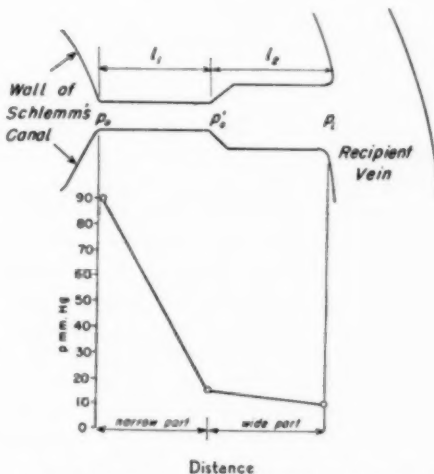
Fig. 3 (Ascher and Spurgeon). Effect of a constriction in an outlet.

in Figure 3, taking $r_1 = 0.0065$ mm., $r_2 = 0.013$ mm., and $l_1 = l_2 = 0.1$ mm. The results are as follows:

$$\Delta p_1 = (p_o - p_o') = 80 \text{ mm. Hg},$$
$$\Delta p_2 = (p_o' - p_i) = 5 \text{ mm. Hg}.$$

The pressure drop along the constriction amounts to 94 percent of the total pressure drop along the tube. The gradients are shown also in Figure 3. It is seen that such a constriction greatly reduces the effectiveness of the tube as a carrier for the aqueous humor. This calculation again illustrates the profound influence of radius changes.

It might be inquired whether the distensibility or elasticity of the primary outlets and the visible aqueous veins would play a part

Fig. 4 (Ascher and Spurgeon). Effect of eccentricity of ellipse on Δp, the pressure drop.

here. Undoubtedly it would, to a limited extent. If the outlet is obstructed, however, or embedded in tissue that strongly resists expansion of the vein (for example, if such tissue is the original cause of the constriction), the elasticity of the tube walls would not help matters very much. Now it is known that the primary outlets are embedded in stiff scleral tissue. The aqueous veins, if superficially located, can be seen to be easily distensible.

So far we have considered only tubes with circular cross section. It is known, however, that the cross sections of many outlets and possibly of aqueous veins is roughly elliptical.[11, 32] For this case Poiseuille's equation

must be modified to the following form:[31]

$$(4) \qquad \frac{Q}{t} = \frac{\pi a^3 b^3 (p_0 - p_L)}{4\eta(a^2+b^2)l}$$

It is known also that the ratio

$$\frac{Q}{t}\bigg]_{(ellipse)} \div \frac{Q}{t}\bigg]_{(circle)}$$

is given by the expression

$$(5) \qquad \frac{2\alpha}{1+\alpha^2}$$

where

$$(6) \qquad \alpha = \frac{b}{a} = \frac{minor\ semiaxis}{major\ semiaxis}$$

This shows that if other factors are the same, the discharge rate from an elliptical tube is less than the rate from a circular tube of the same cross-sectional area.

Equation 4 can be used to calculate the pressure drop for constant values of Q/t, η and l, and for various values of a and b. The results of sample calculations are given in Table 6 and Figure 4. It can be seen, for example, that for a tube of elliptical cross section that is 10 times as wide as it is deep, the pressure drop must be 5 times as great as for a tube of circular cross section and the same cross-sectional area.

The Poiseuille equation shows that a greater pressure must be exerted to force a given amount of liquid of specified viscosity through a long tube than is required for a short tube of the same radius. For example, the pressure drop, Δp, would have to be 5 times as great for a tube 10-mm. long as for one 2-mm. long, other things being equal. In this connection it must be remarked that for very short tubes the Poiseuille equation does not hold rigorously.[30]

The nature of the junction of the outlet tube with Schlemm's canal and with the recipient veins will influence the flow of aqueous liquid. The sharpness or roundness of the corners at the junctions, and the angle of contact between the outlet tube or visible

aqueous vein and the vein into which it empties will be factors of some importance. Their effects, however, will probably amount to a small correction to the Poiseuille equation, and they will not be considered further at this time.

Some of the outlet tubes are highly branched, particularly near the canal. The Poiseuille equation can be applied to each branch, and the entire network can be treated as an arrangement of series and

2 percent per degree, then, using the values given in Table 3, it is found that an increase in pressure of 2.0 mm. Hg is necessary in order to maintain the same rate of flow. Consideration of this temperature influence may help to explain the higher incidence of glaucoma in the cold season of the year.

Finally, we must mention the effect of individual differences and the consequent possibility that, in some individuals, a combination of several of the factors discussed

TABLE 6

EFFECT OF ECCENTRICITY OF ELLIPSE ON ΔP, THE PRESSURE DROP

Major Semiaxis (a in mm.)	Minor Semiaxis (b in mm.)	$\alpha = \dfrac{b}{a}$	Pressure Drop in Elliptic Tube Compared to Pressure Drop in Circular Tube $\dfrac{\Delta p_{el.}}{\Delta p_{cir.}} = \dfrac{1+\alpha^2}{2\alpha}$
0.120	0.01	0.0835	5.99
0.100	0.01	0.100	5.05
0.080	0.01	0.125	4.03
0.050	0.01	0.200	2.60
0.030	0.01	0.333	1.67
0.020	0.01	0.500	1.25
0.017	0.01	0.592	1.14
0.010	0.01	1.00 (circle)	1.00

parallel conductors. Giving illustrative calculations for such a system, however, would merely complicate the presentation of the essential features that we wish to emphasize. Similarly, we will not now discuss the possible effects of bending of the tubes, temperature gradients across an aqueous vein, diffusion or osmotic effects.

The viscosity of the aqueous humor can be of some importance as a factor influencing the rate of discharge. The principal factors that influence the viscosity are the composition (salt, protein, and cell content) and the temperature of the aqueous humor. Increased protein content would result in increased viscosity, that is, in increased resistance to flow. If a considerable length of an aqueous vein is near the surface of the eye so that its contents can be cooled to, say, 10°C. lower than the anterior-chamber temperature, and if we take the increase in viscosity of the liquid (on cooling) to be

above, all working in the same direction, could result in greatly decreased drainage from Schlemm's canal and higher intraocular pressure. Thus, an individual with abnormally few outlet tubes, and with those elliptical and unusually narrow, would be expected to be subject to the development of a dangerous increase of intraocular pressure.

Several times in the preceding discussion of factors that increase the resistance to flow of aqueous humor we have used such expressions as "the pressure in Schlemm's canal must be increased in order to maintain the same rate of flow." We do not mean thereby that a certain outflow rate must necessarily be maintained, as was suggested by Bárány,[19] or that the intraocular pressure must go up by the amounts calculated. The calculations must be considered as illustrative, rather than as giving absolute values, and are given for the purpose of pointing

the way for further research. They show that as the resistance to flow increases, either the intraocular pressure goes up, or the outflow rate goes down, or both. Above all, they show the predominant role played by the number and—especially—by the width of the outlets from Schlemm's canal and of the visible aqueous veins.

No claim is made that the hypothesis of a narrowing of the canal outlets could explain all cases of primary compensated glaucoma; this hypothesis is proposed to stimulate further research, clinical as well as histologic and experimental.

From the surgical viewpoint, sparing of visible aqueous veins during an eye operation seems to be advisable. Gartner[6] is of the same opinion, but De Vries[11] (page 85f.) objected that the aqueous humor, having many collateral pathways available, will find its return into the blood stream anyway. Only where there is a choice for the site of an operation, De Vries would agree to locate it at a place lacking aqueous veins.

Considering the location of the largest outlets from Schlemm's canal in Theobald's plate reconstruction models,[12, 32] we find, in her specimen 705, among 29 outlets only 1 on the nasal and only 3 on the temporal side to have a diameter wider than 100 micra; in specimen 791 there are on either side only two outlets with a cross section of more than 5 cuts, that is, only 4 among 24 outlets. In her specimen 947, there are, among 31 channels, 3 temporal and 2 nasal outlets with a cross section surpassing 5 microscopic cuts.

In other words, all three eyes had only a few large outlets and many smaller ones. If one or more of the large outlets were severed during an operation, they might or might not become replaced by the function of those spared. From the foregoing calculations it is evident that at least a tendency to intraocular-pressure increase will result from the loss of even a few of the larger outlets.

If, for instance, after a cataract incision a very exact readaptation of the wound lips

is secured, a complete recovery of the individual severed outlet is possible but not necessarily to be hoped for. If the original path is not restored, it is doubtful whether the neighboring smaller channels could suffice to substitute for the lost outlet without increase of resistance to the aqueous flow.

Conclusions

The evidence afforded by gonioscopy, on one side, and by biomicroscopy, on the other, is far from complete, and much still remains to be done in all aspects of this subject in connection with the explanation of glaucoma. Histologic verification should be supplied for the working hypothesis that a transient or permanent narrowing of the outlets of Schlemm's canal seems to be connected with, or even may be responsible for, the intraocular pressure increase in eyes suffering from compensated primary glaucoma.

This working hypothesis was arrived at by the following considerations. With increase of intraocular pressure and with a patent fluid-elimination system, a more vigorous fluid elimination should be expected in the aqueous veins of glaucomatous eyes. The bulk of evidence, however, points in an opposite direction, with the clear stream in aqueous veins of glaucomatous eyes neither longer nor wider than in those of eyes with normal intraocular pressure, and with the failure of glaucomatous eyes to show the aqueous-influx phenomenon upon compression of the recipient vessel.

There must be an obstacle somewhere between anterior chamber and biomicroscopically visible veins to explain this discordance. If this impediment were in the trabecular area, a relatively low pressure would prevail inside the canal as compared to the anterior chamber and blood could easily enter the canal of Schlemm. Gonioscopic evidence, however, indicates that, during the stage of high intraocular pressure, no backflow of blood takes place into the

canal despite the fact that, upon compression of the recipient vessel, backflow of blood toward the canal does take place.

The summary of recorded evidence of increment-pressure values, if not invalidated by arbitary omission of high values in eyes with normal pressure, indicates that narrow aqueous veins and those with a narrow root deep in the scleral meshwork need a higher increment pressure, exerted upon the cornea, to become filled with more aqueous humor as compared to wider aqueous veins.

In wide aqueous veins, a slight increment pressure suffices to produce a perceptible increase of aqueous flow. A satisfactory understanding of the recorded increment-pressure values cannot be provided by the simplification attempted by discarding values which do not conform to a preconceived opinion. By this criticism of Goldmann's interpretation, our appreciation for his findings is in no way lessened. However, our attention must be focused on all available data concerning the whole space which is limited by the lining of the anterior chamber on one side, and by the corneal and conjunctival surface on the other. We must consider the normal and the pathologic microscopic anatomy of this region, as well as the physiologic facts about the pressure potentials governing the sanguineous and aqueous contents of the vascular and vessel-like structures in this significant region.

The varying, sometimes oscillating, pressure balance between the two fluids which pass that elimination unit—the canal of Schlemm, its invisible outlets, and the visible aqueous veins—as well as the pathologic changes, anatomic or functional, which may occur in this space and may lead to intra-ocular-pressure increase, must be taken into account.

In eyes with normal intraocular pressure, narrow and wide outlets from Schlemm's canal are found; so are the aqueous-influx phenomenon and the blood-influx phenomenon, and so are backflow of blood into the

canal and missing backflow. High and low increment-pressure readings are also encountered together in the same normal eye yet not in the same individual aqueous vein.

On the other hand, in eyes affected by primary compensated glaucoma, no aqueous-influx phenomenon is observed, no backflow of blood into the canal takes place other than in rare exceptions, and only high increment-pressure values are encountered, even when the eye pressure has been normalized by treatment. The expected narrowing of the canal outlets is still to be proved by histologic examination.

SUMMARY

1. The intraocular-fluid elimination of the human eye can be studied biomicroscopically.

2. A working hypothesis is proposed that, in at least some eyes affected by primary compensated glaucoma, many or all outlets from the canal of Schlemm are narrower than in normal eyes. This hypothesis would explain:

a. The increase of intraocular pressure, due to impaired elimination of aqueous humor.

b. That, in glaucomatous eyes, the clear-fluid stream in aqueous veins and in recipient vessels is neither longer nor wider than in eyes with normal intra-ocular pressure.

c. That, in glaucomatous eyes, compression of a recipient vessel of an aqueous vein fails to produce the aqueous-influx phenomenon.

d. That, in glaucomatous eyes, compression of the recipient vessel results in backflow of blood toward the limbus while blood rarely becomes visible inside the canal of such eyes.

e. That in glaucomatous eyes controlled by either miotics or surgery, compression of the recipient vessel may result in the expulsion of blood from the blocked vessel section.

f. That more pressure needs to be ap-

plied to the globe in order to increase the visible flow of aqueous humor in narrow aqueous veins and in those of glaucomatous eyes.

3. Previous to ocular surgery, aqueous veins should be carefully located and, if possible, they should not be severed during eye operations.

5 West Fourth Street (2).
2034 Dallas Avenue.

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DISCUSSION

DR. P. C. KRONFELD (Chicago, Illinois): This is a very interesting hydrodynamic study, and I can see that several pieces of valid evidence speak in favor of a relative block situated at the level of the outlets of the canal of Schlemm. Dr. Ascher's hypothesis rests more heavily on our findings than we would like to see it at this time. We don't feel that we have settled the matter gonioscopically. It is true that the methods that bring blood into the canal of Schlemm in normal human tissue fail when applied to

eyes with wide-angle glaucoma. One of the reasons is that those methods do not create the same state of relative hypotony in the normal and in the glaucomatous eye.

The simplest method to bring blood into the canal in the normal eye is to lower the intraocular pressure by compression of the globe. That method in the glaucomatous eye brings about a slighter drop in intraocular pressure than in the normal eye and that may be the main reason why the canal doesn't fill with blood in the glaucomatous eye. Therefore, we have continued our work on what might be called angiography on the canal of Schlemm in the wide-angle glaucoma.

All that I wish to say at this time is that there are wide-angle glaucomas in which, by the routine method of compression of the globe, the canal can be made to fill with blood. In the majority of chronic simple glaucomas, however, blood cannot be made to appear in the canal and it is quite possible that Dr. Ascher's explanation applies to the latter group.

DR. ASCHER (closing): I am very happy to hear from Dr. Kronfeld that he agrees to a certain extent with my explanation and I do confess that his experiments, which consisted in withdrawing of aqueous humor, offered some of the leading ideas in my considerations. I think Dr. Kronfeld's experiments are wonderful and deserve further study in comparison with the paralleling changes in the aqueous veins of these particular eyes.

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SEVENTEENTH MEETING

of the

Association for Research in Ophthalmology, Inc.

Proceedings

Business Session

Auditor's Report

Constitution

Officers of the Association

Directory of Members

Geographical List

New Members

Editor

JAMES H. ALLEN, *Iowa City, Iowa*

Publications Committee

PHILLIPS THYGESON, *San Jose, California*

KENNETH C. SWAN, *Portland, Oregon*

V. EVERETT KINSEY, *Boston, Massachusetts*

Committee on Arrangements

WILLIAM A. MANN, *Chairman*

FRANK W. NEWELL   WILLIAM F. HUGHES

Chicago, Illinois

June 21 and 22, 1948

The business session of the Association for Research in Ophthalmology, Inc., convened at 1:45 o'clock in Thorne Hall, Northwestern University, Chicago, Illinois, with Dr. Phillips Thygeson presiding.

DR. PHILLIPS THYGESON (Chairman): Will the meeting please come to order?

For lack of time, we are omitting the minutes of the last meeting. They are available here with the secretary-treasurer and in the *Proceedings*.

I will ask first for the report of the secretary-treasurer.

DR. JAMES H. ALLEN: Mr. Chairman, as of the first of June, 1948, the treasurer listed the following assets:

Cash in bank, First National
Bank, Iowa City $4,246.04
U. S. Treasury Bonds carrying
an interest rate of 2½ percent
at a cost of 4,099.84

Total assets $8,345.88

The Treasury bonds and the interest from them, as you know, are the research medal fund or the Proctor Medal, so that cash in the bank as of the first of June was $4,246.04.

The membership as of the first of June, 1948, carries 21 sustaining members; 320 active members, 8 honorary members, 1 life member, and 42 active members who had not paid their dues as of the first of June. I may say that since the first of June we have received dues from a number of those 42 members. We have at the present time 61 new members to add to this list.

CHAIRMAN THYGESON: I will ask for the report of the auditing committee.

DR. BRITTAIN F. PAYNE: Mr. Chairman, Gentlemen: The committee has examined the financial statement for the year ending May 31, 1948, and finds it in order and recommends its approval. It is recommended that the fiscal year ending May 31 of each year be changed to December 31 each year

to conform with income-tax regulations and membership requirements.

Attention is called to the years 1943 and 1945 when statements were not available due to the wartime inactivity of the association. It is requested that the secretary insert an explanatory footnote at the end of this statement to this effect. (Respectfully submitted, B. F. Payne and R. J. Masters.)

CHAIRMAN THYGESON: You have heard the report of the auditing committee. What is your pleasure? (Motion was made and seconded that the report be accepted; the motion was duly put to a vote, and it was carried.)

CHAIRMAN THYGESON: Next I ask for the report of the committee on the revision of the constitution. As you know, at the meeting last year, certain changes were recommended by the session and these have been studied by the committee who now has a report for your consideration.

DR. KENNETH SWAN: Mr. Chairman, members of the association: it has been the purpose of this revision to strengthen the society by two major changes, namely a change to facilitate the admittance into the society of workers in the basic-science field by establishing a new class of membership entitled the "educational membership." The educational membership, as you will note, provides a special class with reduced annual dues for fulltime workers in research, and for men completing their training.

The second major change is the establishment of sections. It is not the purpose of these sections to provide organizations which will duplicate the functions of the national society but rather to supplement and aid it.

In bringing about these changes, there were some practical problems which necessarily had to be met by compromise. Another major change has already been approved by the society, namely the deletion of the commission. Copies of the revision are in the hands of members. (Respectfully submitted

by Drs. Payne, Berens, Allen, and Swan.)

CHAIRMAN THYGESON: These changes submitted by the committee have been studied by the board of trustees and have been approved by them for submission to the membership. What is your pleasure on these projected changes in the constitution?

DR. POST: I move its acceptance. (The motion was duly seconded, put to a vote, and it was carried.)*

CHAIRMAN THYGESON: There are certain announcements that should be made.

The next meeting has been set for June 6 and 7, 1949, at Philadelphia. The reason for setting Philadelphia has been the difficulty that we had last year in Atlantic City. It was almost impossible to obtain suitable meeting halls.

A Western Section has already been projected in line with the constitutional changes, and an organizational meeting was held last March in San Francisco at which plans were made for a yearly meeting. Dr. Orwyn Ellis of Los Angeles was named chairman and Dr. Michael J. Hogan, secretary.

The Eastern Section organizational meeting has been announced and set for November 13, 1948, at New York at the Lenox Hill Hospital, and the Midwestern Section organization meeting is to be announced in the fall.

The committee on arrangements under the chairmanship of Dr. Mann has done an exceedingly good piece of work for this meeting and I think the association should give him and his committee a vote of thanks.

MEMBER: I so move. (Applause.)

DR. THOMAS D. ALLEN (Chicago): There are certain things that are coming up constantly before the Committee on Optics and Visual Physiology that are highly technical. We would like to have on our committee some of the members of this organization to help us decide some of these problems. I think we ought to empower the trustees to appoint members to the committee as representatives of this association.

DR. CONRAD BERENS (New York City): Mr. Chairman, I think that Dr. Allen has explained things very well indeed. We do need help. The American Committee on Optics and Visual Physiology has asked that this association appoint three members, one for one, one for two, and one for three years on the American Committee on Optics and Visual Physiology.

It seems to me that all we will have to do is to empower you to do that. I would like to move that the trustees be empowered to appoint three members to the American Committee on Optics and Visual Physiology.

DR. THOMAS ALLEN: I second the motion. (The motion was duly put to a vote and carried.)

CHAIRMAN THYGESON: I might announce that at the trustees' meeting, action was taken approving of the report of a committee from the New York Academy of Medicine —I believe that Dr. Berens is chairman— concerning the use of silver-nitrate prophylaxis, and the trustees have requested Dr. James H. Allen, who is making a study of prophylaxis of ophthalmia neonatorium, to report to this society next year.

Dr. Vail, are you ready to make the report of the nominating committee?

DR. DERRICK VAIL (Chicago): Yes. The committee on nominations recommends Dr. Robb McDonald of Philadelphia to be appointed a member of the board of trustees to succeed you, since you are retiring. It also recommends that Dr. James Allen be reelected secretary-treasurer of the organization.

CHAIRMAN THYGESON: You have heard the report of the nominating committee.

DR. CONRAD BERENS: I move thê nominations be closed and the secretary will cast a ballot. (The motion was duly seconded and carried.)

CHAIRMAN THYGESON: The secretary will be asked to cast a ballot. There is no further business before the society, and we will proceed to the first paper of the afternoon. (The business session adjourned at 2:15 o'clock.)

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* See revised version of Constitution, page 259.

We have examined the accounting records of the secretary-treasurer of the Association for Research in Ophthalmology, Inc., Iowa City, Iowa, for the fiscal year ended May 31, 1948. We submit as our report the following statements together with comments thereon:

Exhibit A. Statement of Cash and Securities as of May 31, 1948.

Exhibit B. Statement of Cash Receipts and Disbursements for the fiscal year ended May 31, 1948.

Exhibit C. Statement of Membership as of May 31, 1948.

SCOPE OF EXAMINATION

Cash receipts as recorded in the cash book were traced to the bank deposits for the entire period and were reconciled with the number of members.

Disbursements were verified by examination of paid checks and available supporting invoices and other data. All disbursements appeared to be proper.

Cash in bank was reconciled to the amount reported to us by the depository. We inspected the U. S. Treasury bonds.

On *Exhibit C* is presented a statement of membership as of May 31, 1948. The unpaid dues for 1948 were not confirmed directly with the members.

We have not attempted to determine the number of members who have failed to pay dues prior to 1948, because of the difficulties involved in securing this information, and also because it is our understanding that no attempt will be made to collect these delinquent dues. We were informed that an effort will be made to collect delinquent dues for the fiscal year 1948 and subsequent years.

ACCOUNTANTS' OPINION

In our opinion, the accompanying balance sheet and statement of cash receipts and disbursements fairly present the fund balances of the Association for Research in Ophthalmology, Inc., Iowa City, Iowa, as of May 31, 1948, and the total receipts and disbursements of the association for the fiscal year then ended.

Respectfully submitted,

McGladrey, Hansen, Dunn & Company.

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC.

EXHIBIT A

STATEMENT OF CASH AND SECURITIES

May 31, 1948

ASSETS

Cash in bank—First National Bank, Iowa City, Iowa	$4,246.04
U. S. Treasury bonds—s ¼%, 1967/72 (at cost)	4,099.84
TOTAL ASSETS	**$8,345.88**

NET WORTH

General Fund	$4,234.51
Proctor Medal Fund	4,111.37
TOTAL NET WORTH	**$8,345.88**

EXHIBIT B

STATEMENT OF CASH RECEIPTS AND DISBURSEMENTS

For the Fiscal Year Ended
May 31, 1948

CASH RECEIPTS

1948 Dues:

21 Sustaining Members at $25.00	$ 525.00	
278 Active Members at $5.00	1,390.00	$1,915.00

1947 Dues:

1 Sustaining Member at $25.00	$ 25.00	
37 Active Members at $5.00	185.00	210.00

Total Dues		$2,125.00
Bond Interest		100.00
Sundry Refund		8.50

Total Cash Receipts		$2,233.50

CASH DISBURSEMENTS

Secretary's Salary		$ 283.80
Convention Expense		
Printing Programs	$ 232.56	
Party	601.96	
Projector	54.00	
Public Address System	35.00	
Reporting Meeting	65.00	
Expenses of Secretary-Treasurer	100.00	
Other Convention Expense	12.00	1,100.52

Stationery, Supplies, Printing and Postage		232.59
Founder's Award		131.00
File Cabinet		96.49
Auditing		60.00
Premium — $5,000.00 Position Bond — Secretary-		
Treasurer		25.00
Express Charges		10.51
Safety Deposit Box Rental		3.60
Social Security Taxes		.75

Total Cash Disbursements		1,944.26

EXCESS OF CASH RECEIPTS OVER DISBURSEMENTS		$ 289.24
CASH BALANCE (May 31, 1947)	$3,946.95	
Add: Adjustment to Cash Balance as of May 31, 1947	9.85	

ADJUSTED CASH BALANCE (May 31, 1947)		3,956.80

CASH BALANCE (May 31, 1948) EXHIBIT A		$4,246.04

EXHIBIT C

STATEMENT OF MEMBERSHIP
May 31, 1948

SUMMARY OF MEMBERS

Sustaining 21
Active 320
Honorary 8
Life 1

Total Members 350

MEMBERS BY YEARS

1948 350
1947 306
1946 324
1945 .... Not Available*
1944 283
1943 .... Not Available*
1942 281
1941 279
1940 270
1939 268
1938 272
1937 249
1936 240
1935 245
1934 230
1933 219
1932 203
1931 193
1930 134

UNPAID DUES FOR 1948 42

* Due to wartime inactivity of the association.

CONSTITUTION

ARTICLE I

NAME

The association shall be known as the Association for Research in Ophthalmology, Inc.

ARTICLE II

OBJECTS

The objects of the association are set forth in its application for a charter as follows: To encourage, promote, foster, and assist investigations and research in ophthalmology; in furtherance of the purpose of the corporation to purchase, lease, or otherwise acquire, hold, sell, lease, convey or otherwise dispose of real and personal property or any interest therein; to receive, hold, and invest funds and endowments and to receive and expend the income thereof, and to hold and dispose of such sums of money as may be deemed expedient; and generally to do any and all things which may be necessary or proper in connection with the objects and purposes of the corporation and which may not be contrary to law.

ARTICLE III

MEMBERS

Members of recognized ophthalmologic societies in the United States and Canada and other individuals especially qualified shall be eligible to membership when proposed in writing by a member of the association and shall become members upon election by the Board of Trustees after the recommendation of the committee on admissions, upon payment of the dues hereinafter provided for.

1. Educational Membership. Individuals may be elected to this class of membership during a period of graduate education in ophthalmology or related scientific fields and/or during a period of full-time research. In no instance may an educational membership be held longer than three years without reapplication.

2. Active Membership. Individuals not eligible for educational membership shall be elected to active membership but may choose either this class or sustaining membership.

3. Sustaining Membership. Individuals elected to membership in any class may voluntarily choose to become sustaining members.

4. Life Membership. Upon recommendation of the Board of Trustees and by a majority vote of the members of the association present at its annual meeting, a member may be elected to life membership.

5. Honorary Membership. Upon recommendation of the Board of Trustees and by unanimous vote of the members of the association present at its annual meeting, an individual may be elected to honorary membership.

ARTICLE IV

BOARD OF TRUSTEES

There shall be a Board of Trustees consisting of six members, who shall be elected for a term of six years, and the secretary-treasurer of the association. The secretary-treasurer of the association shall be a member of the Board of Trustees, ex officio. The senior member of the Board of Trustees shall be chairman and in the absence of the chairman the member next in seniority shall act as chairman. At the first meeting of the board, the members shall draw lots for the purpose of determining which of them shall serve for one year, which for two, which for three, which for four, which for five, and which for six years; and the term

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of each member shall come to an end according to the lot which he shall have drawn. At the first annual meeting thereafter, a member of the association shall be nominated for the Board of Trustees by the nominating committee of the association for a term of six years in the place of the member whose term then expires, and thereafter at each meeting a member of the Board of Trustees shall be elected for a term of six years.

ARTICLE V

OFFICERS

The officers of the association shall be a secretary-treasurer and a section secretary and a chairman for each section.

ARTICLE VI

SECTIONS

Regional, national, or international sections of the association may be established by petition of twenty members in various geographical units either within or outside of the United States.

The officers of the sections shall be a section secretary nominated by the secretary-treasurer and approved by the Board of Trustees and a chairman elected by the section.

ARTICLE VII

NOMINATING COMMITTEE

The Board of Trustees shall appoint at each annual meeting a nominating committee of three to serve for the following year. It shall be the duty of the nominating committee to nominate members for the office of secretary-treasurer and one member of the Board of Trustees.

ARTICLE VIII

DUTIES AND POWER OF OFFICERS AND TRUSTEES

The Board of Trustees shall have general charge of the affairs, funds, and property of the association. It shall prepare the programs for the meetings of the association. It shall also appoint a committee on publications and a committee on admissions. It shall elect desirable applicants for membership approved by the committee on admissions. It shall have full power and it shall be its duty to carry out the purpose of the association according to the Charter, Constitution, and By-laws. A majority of its members shall constitute a quorum. Between meetings of the Board of Trustees, the executive power of the association shall be vested in the chairman of the Board of Trustees and the secretary-treasurer.

Chairman of the Board of Trustees. The chairman of the Board of Trustees is the chief executive of the association. He shall preside at all meetings, call all meetings, and perform all duties customary to the office.

Secretary-Treasurer. The secretary-treasurer shall keep a record of the proceedings of all meetings; shall notify officers, trustees, and members of committees of their election; certify official records; keep a list of members; issue notices of all meetings; and perform all duties which may be required of him. He shall have charge of all funds of the association; he shall keep the same and make disbursements therefrom as directed by the Board of Trustees. He shall also obtain two copies of all scientific communications at the time the papers are read. The secretary-treasurer shall furnish bond and have his accounts audited yearly by a certified accountant.

Section Secretary. Section secretaries shall act as assistants to the secretary-treasurer and will serve as secretaries of sectional organizations.

The Section Chairman shall act as assistant to the chairman of the Board of Trustees in the execution of sectional meetings of the association. He shall preside at all meetings of the sections, call all such meetings and perform all executive duties customary to the office.

ARTICLE IX

ELECTION OF OFFICERS

The secretary-treasurer of the association shall be elected by ballot at the annual meeting to serve for one year. A member of the association shall be elected to the Board of Trustees by ballot at each annual meeting to serve for six years. Vacancies occurring in any office shall be filled by the Board of Trustees for the unexpired term until the next annual election.

With the approval of the Board of Trustees, the secretary-treasurer shall appoint a member of each section to act as sectional secretary for one year.

ARTICLE X

MEETINGS

The annual meeting of the association shall be held at a time and place selected by the Board of Trustees.

Sectional meetings shall be held at a time and place selected by the section secretary and chairman and approved by the secretary-treasurer and a member of the Board of Trustees.

ARTICLE XI

AMENDMENTS

Amendments to the Constitution may be made in the following manner: The amendment shall be written and shall be signed by three members of the association and submitted to the Board of Trustees at least thirty days before the annual meeting of the association. At the next annual meeting thereafter the Board of Trustees shall report at the meeting upon said proposed amendment. The amendment shall then be voted upon and two thirds of all the votes cast at the meeting shall be necessary for the adoption of the amendment.

BY-LAWS

ARTICLE I

MEETINGS

Meetings of the association shall be held at such time and place as the Board of Trustees shall determine. Twenty members shall constitute a quorum of the executive sessions of the meetings.

ARTICLE II

COMMITTEE ON ADMISSIONS

The Board of Trustees shall appoint annually a committee upon admissions consisting of three members. The names of all applicants shall be submitted to said committee which shall report its recommendations to the Board of Trustees.

<center>ARTICLE III</center>

DUES

The dues of the association shall be five dollars per annum for an active member and twenty-five dollars per annum for a sustaining member, the fiscal year starting January first. The dues for an educational member shall be two dollars per annum. Dues shall be remitted for life members and honorary members. To defray the expense of sectional meetings, the section secretary may levy dues not to exceed one dollar per annum. The secretary-treasurer, with the approval of the Board of Trustees, may distribute funds to meet unusual expenses of sections. This distribution of funds generally shall be in proportion to the size of the sectional membership.

<center>ARTICLE IV</center>

AMENDMENTS

The By-Laws may be amended in the same manner and with the same procedure as outlined for an amendment to the Constitution.

<center>ARTICLE V</center>

MEETINGS

All executive meetings shall be conducted according to Robert's Rules of Order unless specified otherwise in the Constitution and By-Laws.

OFFICERS OF THE ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY
1948

COMMITTEE ON ADMISSIONS

Lawrence T. Post, M.D. ....St. Louis, Missouri
Francis H. Adler, M.D. ....Philadelphia, Pennsylvania
Frederick C. Cordes, M.D. ....San Francisco, California

OFFICERS OF THE ASSOCIATION FOR
RESEARCH IN OPHTHALMOLOGY
1949

TRUSTEES

Robert J. Masters, M.D. ....Indianapolis, Indiana
Walter H. Fink, M.D. ....Minneapolis, Minnesota
Kenneth Swan, M.D. ....Portland, Oregon
David G. Cogan, M.D. ....Boston, Massachusetts
Brittain F. Payne, M.D. ....New York, New York
P. Robb McDonald, M.D. ....Philadelphia, Pennsylvania

SECRETARY-TREASURER

James H. Allen, M.D. ....Iowa City, Iowa

SECTION SECRETARIES

CANADA
    Clement McCulloch, M.D. ....Toronto, Canada
CENTRAL AND SOUTH AMERICA
    Moacyr E. Alvaro, M.D. ....São Paulo, Brazil
UNITED STATES
  Eastern Section
    Alson E. Braley, M.D. ....New York, New York
  Midwestern Section
    T. E. Sanders, M.D. ....St. Louis, Missouri
  Western Section
    Michael J. Hogan, M.D. ....San Francisco, California
  Southern Section
    Alston Callahan, M.D. ....Birmingham, Alabama

COMMITTEE ON ADMISSIONS

Frederick C. Cordes, M.D. ....San Francisco, California
C. S. O'Brien, M.D. ....Iowa City, Iowa
Parker Heath, M.D. ....Boston, Massachusetts

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY
1948

HONORARY MEMBERS

de Andrade, Cesario, Bahia, Brazil
Berens, Conrad, New York, New York
Duke-Elder, Lady Phyllis, London, England
Duke-Elder, Sir Stewart, London, England

Ferrer, Horatio, Havana, Cuba
Parker, Walter R., Detroit, Michigan
Paton, Leslie, London, England
Weeks, John E., Portland, Oregon

LIFE MEMBER

Rutherford, Cyrus W., Indianapolis, Indiana

SUSTAINING MEMBERS

Allen, James H., Iowa City, Iowa
Castroviejo, Ramon, New York, New York
Chamberlain, Webb Parks, Jr., Cleveland, Ohio
Chan-Pong, Norman Ronald, Trinidad, B.W.I.
Fink, Walter H., Minneapolis, Minnesota
Grant, Hendrie W., St. Paul, Minnesota
Griffey, Edward W., Houston, Texas
Hartenbower, G. E., Bloomington, Illinois
Irvine, Rodman, Beverly Hills, California
Johnson, Lorand V., Cleveland, Ohio
Kirby, Daniel B., New York, New York
Madley, H. Randall, Vallejo, California
Mesirow, M. E., Santa Maria, California
Miller, Miriam, San Francisco, California

Payne, Brittain F., New York, New York
Pischel, Dohrmann K., San Francisco, California
Reese, Algernon B., New York, New York
de Roetth, Andrew F. M., Spokane, Washington
Rychener, Ralph Orlando, Memphis, Tennessee
Shapira, Theodore, Chicago, Illinois
Sheppard, L. Benjamin, Richmond, Virginia
Smith, E. Terry, West Hartford, Connecticut
Taylor, E. Merle, Portland, Oregon
Thomas, Charles I., Cleveland, Ohio
Thomas, Harry V., Clarksburg, West Virginia
Thygeson, Phillips, Los Altos, California
Vanzant, Thomas J., Houston, Texas

DECEASED

Horner, Warren D.

RESIGNED

Meyer, Karl

MEMBERS

A

Adler, Francis H.,[1] 313 S. 17th St., Philadelphia, Pa.
Aiken, Samuel D., 384 Post St., San Francisco 8, Calif.
Albaugh, Clarence H., 727 W. 7th St., Los Angeles 14, Calif.
Allen, James H.,[1-4] University Hospitals, Iowa City, Iowa.
Allen, Lee,[5] University Hospitals, Iowa City, Iowa.
Allen, Thomas D.,[1] 122 S. Michigan Ave., Chicago, Ill.
Alvaro, Moacyr Eyck, 1151 Rua Consolacoa, São Paulo, Brazil.
de Andrade, Cesario,[2] Bahia, Brazil.
Ames, Adelbert, Jr., Dartmouth College, Hanover, N.H.
Armstrong, Richard C., 595 E. Colorado St., Pasadena 1, Calif.
Ascher, Charles K. W.,[1] 2508 Auburn Ave., Cincinnati, 19, Ohio.
Atkinson, Walter S., 129 Clinton St., Watertown, N.Y.
Auten, Hanford Louis,[1] Dartmouth Eye Institute, Hanover, N.H.

[1] Attended 1948 Meeting
[2] Honorary Member
[3] Life Member
[4] Sustaining Member
[5] Educational Member

B

Bahn, Charles A., 1026 Maison Blanche Bldg., New Orleans, La.
Baird, J. Mason, 511 Medical Arts Bldg., Atlanta, Ga.
Balding, Laurence G., 101 S. Madison, Pasadena 1, Calif.
Barkan, Hans, 2351 Clay St., San Francisco, Calif.
Barkan, Otto, 490 Post St., San Francisco, Calif.
Barnett, Irving F., 30 North Michigan Ave., Chicago, Ill.
Bassen, Edward J., 70 E. 66th St., New York, N.Y.
Beach, S. Judd, 704 Congress St., Portland, Me.
Bedell, Arthur J.,[1] 344 State St., Albany, N.Y.
Beetham, William P., 108 Bay State Rd., Boston, Mass.
Bellows, John, 30 N. Michigan Ave., Chicago 2, Ill.
Benedict, William L., Mayo Clinic, Rochester, Minn.
Benson, Clifton E., 515 Sixth St., Bremerton, Wash.
Berens, Conrad,[1-2] 35 E. 70th St., New York, N.Y.
Bettman, Jerome W., 2400 Clay St., San Francisco, Calif.
Black, Nelson M., 703 Huntington Bldg., Miami, Fla.
Blake, Eugene M., 305 Whitney Ave., New Haven, Conn.
Blum, John, 1 Rue Marignac, Geneva, Switzerland.
Bonner, William R., 3 W. White St., Summit Hill, Pa.
Borley, W. E., 450 Sutter St., San Francisco, Calif.
Bothman, Louis,[1] 30 N. Michigan Ave., Chicago, Ill.
Boyd, James L., 10 Edge Hill Rd., Glen Cove, L.I., N.Y.
Boyes, Truman L., 654 Madison Ave., New York, N.Y.
Braley, Alson E.,[1] 635 W. 165th St., New York, N.Y.

Brandenburg, K. C., 110 Pine Ave., Long Beach, Calif.
Brault, Jules, 418 E. Sherbrooke St., Montreal, Canada.
Bribach, E. J., 603 Commercial St., Atchinson, Kan.
Bronk, Henry N., 321 E. Tremont Ave., New York 57, N.Y.
Brown, Albert L., 1137-38 Carew Tower, Cincinnati, Ohio.
Brown, E. V. L.,[1] 122 S. Michigan Ave., Chicago, Ill.
Bruner, Abram B., 1214 Guardian Bldg., Cleveland, Ohio.
Bruner, William E., 1214 Guardian Bldg., Cleveland, Ohio.
Budd, Francis X., 4240 W. 58th St., Cleveland, Ohio.
Buffington, W. R., 1206 Hibernia Bank Bldg., New Orleans, La.
Bulson, Eugene L., 347 W. Berry St., Fort Wayne, Ind.
Burch, Edward P., 424 Hamm Bldg., St. Paul, Minn.
Burch, Frank E., 424 Hamm Bldg., St. Paul, Minn.
Burian, Hermann M., 520 Commonwealth Ave., Boston 15, Mass.
Burke, John W., 1740 M St., N.W., Washington, D.C.
Burr, Sherwood P., Jr.,[5] 1629 Truxtun Ave., Bakersfield, Calif.
Buschke, William H., 138-52 Jewel Ave., Flushing, N.Y.
Byrnes, Victor Allen, 278 W. Wildwood Dr., San Antonio, Tex.

C

Calhoun, F. Phinizy, 478 Peachtree St., Atlanta, Ga.
Callahan, Alston,[1] Dept. of Ophthalmology, University of Alabama Medical College, Birmingham, Ala.
Campion, George Stuart, 490 Post St., San Francisco, Calif.
Carrasquillo, Honorio F.,[1] Medical Arts Bldg., San Juan, Puerto Rico.
Carroll, Frank D., 635 W. 165th St., New York, N.Y.
Cary Edward H., 631 Medical Arts Bldg., Dallas, Tex.
Casten, Virgil C., 412 Beacon St., Boston, Mass.
Castroviejo, Ramon,[4] 9 E. 91st St., New York, N.Y.
Chace, Robert R., 635 W. 165th St., New York 32, N.Y.
Chalfant, W. Paxson, Jr., 1915 Sixteenth St., N.W., Washington, D.C.
Chamberlain, Webb Parks, Jr.,[4] 7405 Detroit Ave., Cleveland, Ohio.
Chandler, Paul A., 5 Bay State Rd., Boston, Mass.
Chan-Pong, Norman Ronald,[4] 88 Frederick St., Port-of-Spain, Trinidad, B.W.I.
Chapman, Vernon A., Palm Springs, Calif.
Clapp, Clyde A.,[3] 513 N. Charles St., Baltimore, Md.
Clark, Cecil P., 23 E. Ohio St., Indianapolis, Ind.
Clark, William B., 200 Carondelet St., New Orleans, La.
Clothier, William L., 407-411 Kane Bldg., Pocatello, Idaho.
Cloutier, Roland, 50 Haven Ave., New York 32, N.Y.
Cogan, David G.,[1] 243 Charles St., Boston, Mass.
Cohen, Martin, 29 E. 64th St., New York, N.Y.
Colson, Z. William, 501 Essex St., Lawrence, Mass.
Constantine, F. H., 17 E. 72nd St., New York, N.Y.
Constantine, K. W., 229 Barton Ave., Palm Beach, Fla.
Cordes, Frederick C., 384 Post St., San Francisco, Calif.
Courtney, R. H., 501 E. Franklin St., Richmond, Va.
Courvoisier, Earl A., 55 E. Washington St., Chicago, Ill.
Covey, John Knox, 140 W. High St., Bellefonte, Pa.
Craig, Paul C., 232 N. 5th St., Reading, Pa.
Crawford, H. C. Orr Doctors Bldg., Atlanta, Ga.
Crawford, Joseph William, 490 Post St., San Francisco, Calif.
Cregar, John S., 440 Harrison St., East Orange, N.J.
Crisp, William H., 1276 Emerson St., Denver, Colo.
Cross, George H., 525 Welsh St., Chester, Pa.
Culler, Arthur M.,[3] 150 E. Broad St., Columbus, Ohio.
Cummings, Mrs. Edith L. W., 429 New Budge Rd., Bergenneld, N.J.
Cushman, Beulah,[3] 25 E. Washington St., Chicago, Ill.
Cutler, Morton, Medical Arts Bldg., Twin Falls, Idaho.

D

Dasilva, Antonio Isidore, Rua Santa Catarina 1011, Belo Horizonte, Minas Gerais, Brazil, South America.
Dean, Alfred, 26 Sheldon Ave., Grand Rapids, Mich.
De Ocampo, Geminiana, Philippine General Hospital, Manila, P.I.
DeVoe, Arthur Gerard, 635 W. 165th St., New York, N.Y.
Dewey, C. H., 760 S. Oak Knoll, Pasadena, Calif.

DeWitt, Edward N., 1600 N.E. 4th Pl., Fort Lauderdale, Fla.
Dickson, Owen C., 2628 Telegraph Ave., Berkeley, Calif.
Dillahunt, Jack A.,[8] University Hospitals, Iowa City, Ia.
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Duane, T. D.,[1] 215 S. Dodge St., Iowa City, Iowa.
Duke-Elder, Lady Phyllis,[2] London, England.
Duke-Elder, Sir Stewart,[2] London, England.
Dunnavan, Floyd L., Suite 514 Medical Arts Bldg., Vancouver, Wash.
Dunnington, John H., 635 W. 165th St., New York, N.Y.

E

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Elliott, Alfred J., 170 St. George St., Toronto 5, Canada.
Ellis, Orwyn H.,[3] 727 W. 7th St., Los Angeles 14, Calif.
Elvin, Norman L., 309 Medical Arts Bldg., Winnipeg, Manitoba, Canada.
Engel, Samuel, 350 Post St., San Francisco, Calif.
Evans, John N., 23 Schermerhorn St., Brooklyn, N.Y.
Evans, Samuel Davidson, 1502 Park Bldg., Pittsburgh, Pa.
Evans, William Hiram, 510 Dollar Bank Bldg., Youngstown, Ohio.

F

Ferrer, Horatio,[2] Havana, Cuba.
Fine, Max, 655 Sutter St., San Francisco 2, Calif.
Fink, Austin I., Valley Forge General Hospital, Phoenixville, Pa.
Fink, Walter H.,[1-4] 1029 Medical Arts Bldg., Minneapolis 2, Minn.
Fonda, Gerald Emmett, Milburn Theater Bldg., 350 Milburn Ave., Milburn, N.J.
Foote, Franklin M.,[3] 1790 Broadway, New York, N.Y.
Fralick, F. Bruce, 408 First National Bank Bldg., Ann Arbor, Mich.
Freeman, Sheldon B., 196 Linwood Ave., Buffalo, N.Y.
Friedenwald, Harry, 1212 Eutaw Pl., Baltimore, Md.
Friedenwald, Jonas S.,[1] 1212 Eutaw Pl., Baltimore, Md.
Friedman, Benjamin, 6 W. 77th St., New York, N.Y.
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G

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Gifford, Harold, 1620 Medical Arts Bldg., Omaha, Neb.
Gill, Earl King, 323 Medical Arts Bldg., San Antonio, Tex.
Gill, William D., 323 Medical Arts Bldg., San Antonio, Tex.
Gillette, David F., 109 S. Warren St., Syracuse, N.Y.
Givner, Isadore, 108 E. 66th St., New York 16, N.Y.
Goar, Everett L.,[1] 1304 Walker Ave., Houston, Tex.
Goldberg, Sol, 8082 Jenkins Arcade, Pittsburgh, Pa.
Goodfellow, Thomas John, 20 Arcade Bldg., Saratoga Springs, N. Y.
Gradle, Harry S., 14060 Valley Vista Blvd., Sherman Oaks, Calif.
Grant, Hendrie W.,[4] 330 Lowry Medical Arts Bldg., St. Paul Minn.
Gray, John Edward, 430 36th St., Sacramento, Calif.
Green, John, 3720 Washington Blvd., St. Louis, Mo.
Gresser, Edward B., 39 E. 75th St., New York, N.Y.
Griffey, Edward W.,[4] 1022 Medical Arts Bldg., Houston, Tex.
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Guibor, George, 30 N. Michigan Ave., Chicago, Ill.
Gundersen, Trygve,[1] 5 Bay State Rd., Boston, Mass.
Guy, Loren P., 40 E. 62nd St., New York, N.Y.
Guyton, Jack S., Johns Hopkins Hospital, Baltimore 5, Md.

H

Haessler, F. Herbert, 561 N. 15th St., Milwaukee, Wis.
Hanson, A. George, 1528 Medical Dental Bldg., Seattle 1, Wash.
Harbridge, Delamere, 12 N. Central Ave., Phoenix, Ariz.
Hardesty, John F., 634 N. Grand Blvd., St. Louis, Mo.
Hardy, LeGrand H., 23 E. 79th St., New York, N.Y.
Hare, Robert, 416 N. Bedford Dr., Beverly Hills, Calif.

Ogle, Kenneth N., (Ph.D.), Mayo Clinic, Division of Physics and Biophysical Research, Rochester, Minn.
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O'Rourke, Donald H., 920 Republic Bldg., Denver 2, Colo.
Osler, Jay Kershner, 150 State St., Bangor, Me.
Owens, William C., Johns Hopkins Hospital, Baltimore 5, Md.

P

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Pfingst, Harry Adolph, 1014 E. 102nd St., Cleveland, Ohio.
Phillips, Josephine Dirion, 2010 E. 102nd St., Cleveland, Ohio.
Pichette, Henri, 425 St. John St., Quebec City, Quebec, Canada.
Pischel, Dohrmann K.,[4] 490 Post St., San Francisco, Calif.
Plumer, John S., 121 University Pl., Pittsburgh, Pa.
Post, Lawrence T.,[1] 508 N. Grand Blvd., St. Louis, Mo.
Post, Martin Hayward, Jr.,[2] 520 Metropolitan Bldg., St. Louis, Mo.
Potter, William Bentley,[1] 816 Strand, Galveston, Tex.
Prangen, Avery D.,[1] Mayo Clinic, Rochester, Minn.

R

Raffo, Julio C., Gremios No. 465, Lima, Peru, South America.
Rasgorshek, Robert H.,[1] 425 Aguila Court, Omaha, Neb.
Reeder, James E., Jr., 523 Davidson Bldg., Sioux City 13, Iowa.
Redding, Willis A., Towanda, Pa.
Reeh, Merrill John, 4212 N.E. Broadway, Portland 10, Ore.
Reese, Algernon B.,[1-4] 73 E. 71st St., New York, N.Y.
Regan, James J., 520 Commonwealth Ave., Boston, Mass.
Reid, Frederick K., 500 N. George St., Rome, N.Y.
Reid, Horace W., 2205 Union Central Bldg., Cincinnati, Ohio.
Reid, John J., Jr., 105 E. 63rd St., New York 21, N.Y.
Rigg, James P., 521 Rood Ave., Grand Junction, Colo.
Robbins, Alfred R., 1930 Wilshire Blvd., Los Angeles, Calif.
Roberts, Walter L.,[1] 8225 Ramsgate, Los Angeles, Calif.
Rodin, Frank H., 490 Post St., San Francisco, Calif.
de Roetth, Andrew F. M.,[1-4] 1006 Overbluff, Spokane, Wash.
Romaine, Hunter, 111 E. 65th St., New York, N.Y.
Romejko, Walter J., 1810 K St., N.W., Washington 6, D.C.
Rones, Benjamin, 1601 Eye St., N.W., Washington, D.C.
Roper, Kenneth Lawrence,[1] 58 E. Washington St., Chicago, Ill.
Rosenthal, Benjamin C., 140 New York Ave., Brooklyn, N.Y.
Rosner, Robert Samuel,[1] 10300 Carnegie, Cleveland 6, Ohio.
Ross, Cecelia, 1318 Second St., Santa Monica, Calif.
Row, Hamilton D., 906 Hume-Mansur Bldg., Indianapolis, Ind.
Rowland, Louise Sloan, Wilmer Institute, Johns Hopkins Hospital, Baltimore, Md.
Rowland, William M., 1118 St. Paul St., Baltimore, Md.
Ruedemann, A. D., Wayne University, Detroit, Mich.
Rutherford, Cyrus W.,[3] 4601 N. Pennsylvania St., Indianapolis, Ind.
Ryan, William F., 520 Commonwealth Ave., Boston, Mass.
Rychener, Ralph Orlando,[1-4] 130 Madison Ave., Memphis, Tenn.

S

Sachs, Erich,[1] 913 W. Agatite St., Chicago, Ill.
Samuels, Bernard, 57 W. 57th St., New York, N.Y.
Sanders, T. E.,[1] 508 N. Grand Blvd., St. Louis, Mo.
Scala, Norman Philip, 1201 Nineteenth St., N.W., Washington, D.C.
Schachat, Walter S., 30 E. 60th St., New York, N.Y.
Scheie, Harold G.,[1] 313 S. 17th St., Philadelphia 3, Pa.

Schlaegel, Theodore F., Jr.,[1] Indiana University Medical Center, Indianapolis, Ind.
Schmerl, Ernest,[1] Toledo Hospital, Institute of Medical Research, 2805 Oatis Ave., Toledo, Ohio.
Scholz, Roy O., 11 E. Chase St., Baltimore, Md.
Schultz, Jacob F., 1304 Walker Ave., Houston, Tex.
Schuster, Stephen A., First National Bank Bldg., El Paso, Tex.
Scobee, Richard G., 640 S. Kingshighway, St. Louis, Mo.
Schaffer, Robert N., 490 Post St., San Francisco 2, Calif.
Shahan, Philip T., 508 N. Grand Blvd., St. Louis 3, Mo.
Shahan, William E., 508 N. Grand Blvd., St. Louis 3, Mo.
Shannon, C. E. G., 1930 Chestnut St., Philadelphia, Pa.
Shapira, Theodore,[1-4] 109 N. Wabash Ave., Room 1920, Chicago, Ill.
Sharbaugh, George B., 212 W. State St., Trenton, N.J.
Sheard, Charles, Mayo Clinic, Rochester, Minn.
Sheppard, L. Benjamin,[4] Medical Arts Bldg., Richmond, Va.
Sherman, A. Russell, 671 Broad St., Newark, N.J.
Sherman, Elbert S., 671 Broad St., Newark, N.J.
Siegel, Edward, 45 Oak St., Plattsburgh, N.Y.
Simonton, John T., 108-41 63rd Dr., Forest Hills, L.I., N.Y.
Sitchevska, Olga, 30 Fifth Ave., New York, N.Y.
Sitney, Julian J., 4063 Radford Ave., Studio City, Calif.
Sloan, Henry L., 6 W. 7th St., Charlotte, N.C.
Smith, Byron, 927 Park Ave., New York, N.Y.
Smith, E. Gerard, 339 N. Duke St., Lancaster, Pa.
Smith, E. Terry,[4] P.O. Box 42, West Hartford, Conn.
Smith, Hiram J., 30 N. Michigan Ave., Chicago, Ill.
Smith, Homer E., 54 E. S. Temple St., Salt Lake City 1, Utah.
Smith, James W., 1016 Fifth Ave., New York 28, N.Y.
Smith, Joseph G., 450 Sutter St., San Francisco, Calif.
Snell, Albert C., 53 S. Fitzhugh St., Rochester, N.Y.
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